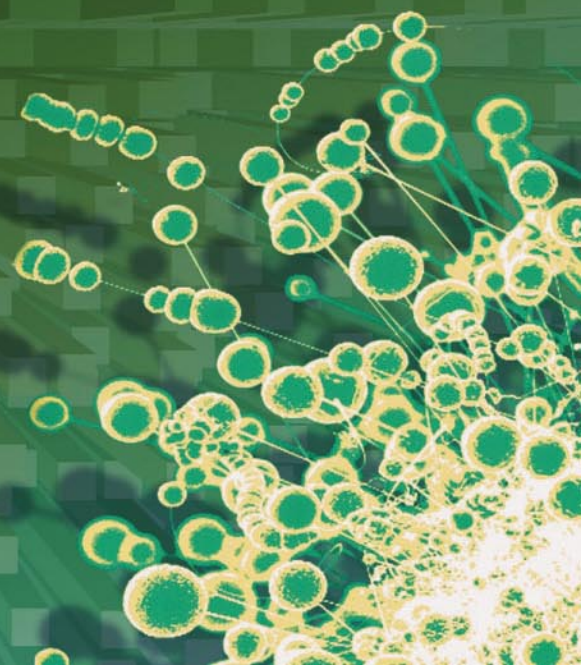
The National Nanotechnology Initiative

Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials



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About this document

The primary purpose of this document is to identify for the Federal Government environmental, health, and safety (EHS) research and information needs related to understanding and management of potential risks of engineered nanoscale materials that may be used, for example, in commercial or consumer products, medical treatments, environmental applications, and research. This document will be used by NSTC's Nanoscale Science, Engineering, and Technology (NSET) Subcommittee and Federal agencies to inform and guide research programs. It also communicates to various nongovernment stakeholders approaches for obtaining the knowledge and understanding necessary to enable risk assessment and management of nanomaterials. Industry producers and users of nanomaterials, for example, may use this document to inform their own research, risk assessment, and risk management activities. The document was prepared by members of NSET's Nanotechnology Environmental and Health Implications (NEHI) Working Group, with assistance from NNCO staff members.

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Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials

September 2006

Nanoscale Science, Engineering, and Technology Subcommittee
Committee on Technology
National Science and Technology Council

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EXECUTIVE OFFICE OF THE PRESIDENT
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September 20, 2006

Dear Colleague:

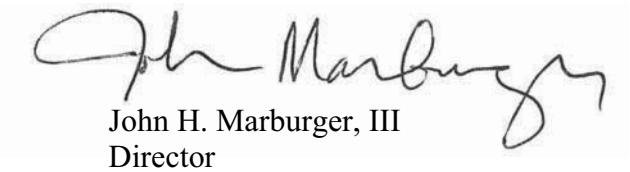
Important scientific and technological advances based on understanding and control of properties and processes at the scale of atoms and molecules—the nanometer scale—are taking place in laboratories around the world. The ability to control materials at the nanoscale is already leading to novel materials and improved performance and other characteristics in existing products. Over the longer term, nanotechnology promises even more revolutionary advances with potential impacts on nearly every industrial sector, including energy, health care, defense, transportation, and electronics. The novelty of nanoscale materials arises from the fact that with decreasing size, the properties of materials change. Such changes, however, may be accompanied in some cases by increased environmental, health, and safety risks.

This report identifies the research and information needed in order to enable sound risk assessment and risk management of nanoscale materials and the products that incorporate them. It was prepared by the Nanotechnology Environmental and Health Implications Working Group under the National Science and Technology Council's Nanoscale Science, Engineering, and Technology Subcommittee. Its primary purpose is to inform Federal agencies that support nanotechnology research to guide planning, management, and coordination of nanotechnology-related environmental health and safety research. These efforts will also support agencies responsible for protecting public health, workers, consumers, and the environment, and guide other stakeholders, including manufacturers and users of nanoscale materials, in their own health and safety activities.

The National Nanotechnology Initiative (NNI) has recognized the need to understand the potential health and environmental effects of nanoscale materials and has funded research in this area since its inception. In Fiscal Year 2007, the President's Budget requests $44 million for research that is aimed primarily at understanding and addressing the potential risks to health and the environment posed by nanotechnology. In addition, the NNI funds significant research into the development of instruments and methods for characterizing nanoscale materials and processes that are critical to the ability to perform accurate health and safety testing.

Today, the United States leads the world not only in spending for nanotechnology development but also, by an even larger margin, in its investment in research to understand the potential health and safety issues. Continued strong interagency coordination of the Federal Government's investment in both aspects of this emerging technology will help ensure full realization of the potential of nanotechnology in a safe and responsible manner.

Sincerely,



John H. Marburger, III
Director

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Executive Summary

Scientific and engineering advances in the understanding and control of matter at the scale of 1–100 nanometers (nm) are the realm of "nanotechnology." Within this realm is the potential for achieving significant practical benefits in applications areas ranging from energy and electronics to medicine and agriculture. The range and magnitude of possibilities that emerge from the ability to design and manufacture materials and increasingly complex structures and devices at the scale of atoms and molecules is great, leading many to believe that nanotechnology may revolutionize technology as we know it. At the nanoscale material properties vary as a function of size, which not only enables new benefits, but also may lead to unintended health and environmental risks. This document provides a description of the research needed in order to identify and address potential risks from the application and use of nanotechnology.

The Federal Government's nanotechnology research programs, in general, fall under the National Nanotechnology Initiative (NNI). Coordination of research in the field takes place through the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council.

In order to support Federal activities to protect public health and the environment, the NSET Subcommittee created the Nanotechnology Environmental and Health Implications (NEHI) Working Group in 2003 with the purpose, among other things, of facilitating the identification, prioritization, and implementation of research and other activities required for the responsible research, development, utilization, and oversight of nanotechnology.

This document reflects the efforts of the NEHI Working Group to begin this facilitation process and, specifically, to describe the environmental, health, and safety (EHS) research and information needed to enable sound risk assessment and risk management decision making. The document has been produced collaboratively by the Federal agencies that participate in the NNI and has been informed by recommendations from industry liaison groups and by other reports and documents on EHS research needs.

The primary purpose of this document is to identify for the Federal Government the EHS research and information needs related to understanding and management of potential risks of engineered nanoscale materials that may be used in commercial or consumer products, medical treatments, environmental applications, research, or elsewhere. In addition, industry producers and users of engineered nanoscale materials may use this document to inform their own research, risk assessment, and risk management activities. Through this publication, the NSET Subcommittee communicates to various nongovernmental stakeholders the research needs and approaches that it has identified for obtaining the knowledge and understanding necessary to enable risk assessment and management of engineered nanoscale materials.

The NSET Subcommittee and Federal agencies will use this document to inform and guide individual and joint research programs. The next steps toward addressing the research needs described in this document include further prioritization among the identified needs, evaluating in greater detail the NNI EHS research portfolio, determining gaps between identified research needs and the research already underway, coordinating and facilitating among NNI agencies' research programs to address outstanding priorities, and establishing a process for periodic review of progress for updating research needs and priorities. The NSET Subcommittee will seek stakeholder input regarding strategic and interim goals for filling the EHS information needs and gaps for engineered nanoscale materials.

This document addresses EHS research needs associated only with engineered nanoscale materials. It does not address nanoscale materials that are naturally occurring or are incidental byproducts of manufacturing, combustion, or other human processes. However, the substantial body of knowledge about risks related to exposures to these other categories of nanoscale materials will inform risk assessment and management for engineered nanoscale materials.

That a new technology potentially could offer both benefits and, at the same time, potential risk is not unique to nanotechnology, but rather is a phenomenon associated with many new technologies. Even existing technologies and products have associated risks; two common examples are electric power and medical X-rays. Learning more about risks of technologies allows for their successful management and the realization of their benefits.

Key Document Terms

Engineered nanoscale materials, or nanomaterials, are those that have been purposefully manufactured or synthesized to have a size with at least one dimension in the range of approximately 1–100 nm and that exhibit unique properties determined by this size. *In this document, when the term "nanomaterials" is used alone, it refers to engineered nanoscale materials.*

The acronym "EHS" will be used in this document as shorthand for the collection of fields associated with the terms "environmental health, human health, animal health, and safety" when used in the context of risk assessment and risk management. While a variety of acronyms derived from permutations of the terms environment, health, and safety exist in the scientific and public health policy literature, "EHS" within this document has just one interpretation, as stated above.

The contextual framework for this document, including an overview of nanotechnology and risk characterization, is provided in Chapter 1. This chapter includes a discussion of the principles for identifying and prioritizing nanomaterials EHS research so as to optimize the usefulness of research results. The chapter also describes how this document fits into the overall process by which the NSET Subcommittee is coordinating nanomaterials EHS research and describes the next steps for prioritizing, addressing, and updating the research needs.

Chapters 2-6 each address specific areas of scientific investigation for assessing and managing potential EHS risks of nanomaterials. Each chapter provides detail on existing Federal activities in the area, lists a consensus opinion on the priority research needs within the area and, for most of the areas, offers informed options for future research to address the identified needs.

Descriptions of the five general research areas identified by the NNI agencies as necessary for evaluating EHS issues for nanomaterials and examples of EHS research needs for each general area follow. *This document identifies priority research but does not prioritize within or among the research categories leaving that as a next step. The sequence of chapters does not reflect prioritization among the categories.*

Instrumentation, Metrology, and Analytical Methods

Chapter 2 describes research needs for new instrumentation and standard measurement protocols, as well as the development of reference materials and data related to the detection, characterization, and measurement of physical, chemical, and biological properties of engineered nanoscale materials in environmental and biological matrices (e.g., air, water, soil, cells, tissues, organs, organ systems, and whole organisms). Also addressed is the development of terminology, nomenclature, and standards.

Identified research and information needs in this area include

- methods for detecting nanomaterials in biological matrices, the environment, and the workplace
- methods for standardizing particle size and size distribution assessment
- methods and standardized tools for assessing nanomaterial shape, structure, and surface area
- an inventory of engineered nanomaterials and their uses

Nanomaterials and Human Health

Chapter 3 identifies research needed to determine the biological response to engineered nanoscale materials and their byproducts, the results of which may contribute to identifying potential adverse health effects in humans. This includes research on subcellular components, cells, tissues, organ systems, and whole organisms to determine biocompatibility and toxicity of various engineered nanoscale materials, and research to evaluate current toxicity screening tests and develop new tests as needed. Identified research and information needs in this chapter include

- understanding of the absorption and transport of nanomaterials throughout the body from different routes of exposure including oral, inhalational, dermal, and intravenous
- understanding of the properties of nanoscale materials that elicit a biological response
- identification and/or development of appropriate *in vitro* and *in vivo* assays/models to predict *in vivo* human responses to nanomaterial exposure
- methods to quantify and characterize exposure to nanomaterials in biological matrices

Nanomaterials and the Environment

Chapter 4 focuses on research aimed at identifying, understanding, and controlling the potential effects of engineered nanoscale materials on both relevant ecological receptors and the ecosystems that they occupy and research on ultimate disposition and transport of engineered nanoscale materials that leads to a better understanding of the mechanisms by which nanoscale materials enter, remain in, degrade, and are transported through environmental media. Identified research and information needs in this area include

- evaluation of testing schemes for ecological effects
- identification of factors affecting the transport of nanomaterials in the environment
- understanding of the transformation of nanomaterials under different environmental conditions

Health and Environmental Surveillance

Chapter 5 addresses research on the systematic collection, analysis, and interpretation of data obtained over time on human exposure to nanomaterials in the workplace and other indoor and outdoor environments; research to determine the presence of these materials or their byproducts in the environment; research on the determinants of exposures to support interpretation of limited or surrogate workplace and environmental data; monitoring of the health experience of individuals exposed to nanomaterials; and monitoring of outcomes in habitats impacted by nanomaterials. Identified research and information needs in this area include

- understanding of workplace processes and factors that affect exposure to nanomaterials
- quantification of nanomaterial exposure to the general population from industrial processes, consumer products, and other products containing nanomaterials
- establishment of environmental monitoring protocols

Risk Management Methods

Chapter 6 covers research on methods for risk management of nanomaterials, including research on methods to reduce exposures to potentially hazardous nanomaterials; research to improve procedures for risk and accident avoidance; research to improve work practices, engineering controls, and protective equipment; and research to develop procedures for life cycle assessment and improved understanding of potential impacts over the full product life cycle, from raw material extraction through disposal and/or recycling. Identified research and information needs in this area include

- improved understanding of the unique challenges for process design and engineering control systems applied to airborne engineered nanoscale materials
- understanding and development of manufacturing approaches that minimize environmental impact to enable "green design" principles
- determination of the stages in a product's life cycle that introduce potential for EHS risks
- evaluation of whether current risk communications methods are adequate for known risks and for risks that can be anticipated from currently available information

Federal Government Support for EHS Research

The NNI has recognized the importance of EHS research from its inception in 2001. Government-funded research toward understanding the EHS implications of nanomaterials generally falls into three broad areas: research on fundamental properties and processes of nanomaterials that can lead to the understanding of broad classes of materials in various environments and applications, development of metrology tools and methods for measuring exposure to and for characterizing nanomaterials, and research on toxicological properties and health effects of nanomaterials that are expected to be used widely in commerce.

Funding for nanotechnology-related EHS research has grown since it was first tracked in 2005. That year, approximately $35 million was devoted to research with the primary purpose of understanding and addressing potential risks to health and the environment posed by this technology. The estimated investment in this research for 2006 is $38 million, and the President's 2007 budget request calls for increasing the amount to $44 million.

In 2007, the following agencies requested funding for EHS research: National Institutes of Health (NIH), National Institute for Occupational Safety and Health (NIOSH), National Institute of Standards and Technology (NIST), Department of Defense (DOD), Environmental Protection Agency (EPA), National Science Foundation (NSF), and United States Department of Agriculture (USDA) Cooperative State Research, Education and Extension Service (CSREES). These research programs, along with other activities related to promoting the understanding of EHS implications of nanotechnology, are coordinated through the NEHI Working Group and its parent body, the NSET Subcommittee. Specifics of these programs and activities can be found in the NNI Supplement to the President's 2007 Budget (see www.nano.gov/NNI_07Budget.pdf).

In addition to the Federal Government, other stakeholders are involved in this area of research. Manufacturers of nanomaterials and related products have a responsibility to test specific products for safety and to assess workplace safety and provide health surveillance. It is clear that not only is coordination of research activities among the NNI agencies important, but also collaboration with industry and with other governments will be necessary in order to expedite progress.

Next Steps

In order to expedite progress toward addressing the research needs described in this document and to adjust those needs as development, understanding, and use of nanomaterials advance, the NSET Subcommittee—in part through the efforts of the Nanotechnology Environmental and Health Implications (NEHI) Working Group—will continue to work with the NNI agencies. To recapitulate, the next steps are as follows:

- further prioritize research needs among those identified in this report
- evaluate in greater detail the current NNI EHS research portfolio
- perform a "gap analysis" of the NNI EHS research compared to the prioritized needs
- coordinate and facilitate among the NNI agencies' research programs to address priorities
- establish a process for periodic review of progress and for updating the research needs and priorities

Continued coordination among the agencies participating in the NNI, in consultation and collaboration with other stakeholders, will facilitate efforts toward achieving these next steps and performing the research outlined in this report. Conducting research bearing on EHS in parallel with the development of nanomaterials and their applications will help to ensure the full, safe, and responsible realization of the promise of nanotechnology.

1 Introduction

BACKGROUND TO THIS DOCUMENT

Nanotechnology—scientific and engineering advances in the understanding and control of matter at the scale of 1–100 nanometers (nm)—will likely be the foundation for achieving widespread benefits, including smarter electronics, improved health, advanced agriculture, and cleaner sources of energy. The magnitude of possibilities for exploiting nanotechnology is great—ranging from the ability to design and manufacture materials at the scale of atoms and molecules to the development of increasingly sophisticated active structures, devices, and systems. These possibilities lead many to believe that nanotechnology may revolutionize technology as we know it.

Many of the potential benefits of nanotechnology arise from the fact that engineered nanoscale materials exhibit chemical, physical, and biological properties and behavior different from those of the same materials in bulk or macroscopic form. For example, gold, which is valued for its inert properties at the macroscale, becomes highly reactive when prepared as 3 nm particles; and many bulk semiconductor materials are very poor light emitters, but nanometer-sized semiconductor "quantum dots" can be made to fluoresce brilliantly in various colors depending on their size.

In addition to nanoscale versions of existing materials, entirely new classes of materials, such as new forms of carbon, called fullerenes, have been developed, offering unique sets of properties. The most familiar of these are carbon spheres known as C_{60}, also called buckyballs, and their elongated siblings, carbon nanotubes. Carbon nanotubes are among the strongest materials known. They can exhibit nonconducting, semiconducting, or metallic electronic properties depending on their structural configuration.

These novel properties exhibited by engineered nanoscale materials not only enable new benefits but also may lead to unintended health and environmental risks. This document provides a description of research needed in order to identify and address potential risks from the development of nanotechnology.

Nanomaterials have contributed to developments in diverse application areas, such as medical imaging, catalysis, and solid state lighting. Products on the market today are enabled by nanomaterials, including stain-resistant clothing and glare-resistant sunglasses. Although researchers envision complex devices made of nanoscale components with novel capabilities, at present most products offer modest improvements in performance by incorporating nanomaterials.

Scientific understanding of how engineered nanoscale materials of various compositions interact with biological systems is incomplete. There are fundamental questions that research must address about how to best assess the impacts of nanomaterials. Questions include: Are current toxicity testing methods appropriate for assessing the toxicity and potential biological effects of engineered nanoscale materials? How do chemical/physical properties of those nanomaterials relate to their elicited biological responses? What kinds of human and environmental exposures to nanomaterials can be anticipated and measured? By which paths do nanomaterials move within the body? Are there any special considerations for the measurements of nanomaterials?

These and more specific research questions are discussed in this document. The research itself is expected to be funded by governments, including the U.S. Government, and by non-governmental institutions, both academic and industrial. The U.S. Government research will take place within the framework of the National Nanotechnology Initiative (NNI) Strategic Plan, set out in 2004 (see www.nano.gov/NNI_Strategic_Plan_2004.pdf).

As research—both publicly and privately supported—on applications of nanomaterials continues to expand, it is important to carry out the research that will enable well-informed risk assessment. It is incumbent upon those responsible for managing product and process risks and for protecting human and environmental health to utilize available information to assess risk. Where information is not available, it is important that experts in the fields—e.g., manufacturers, regulators, standards developers, research agencies and institutions—identify the types of information and research that are needed and to fill any gaps that exist. Sharing of data and collaboration on research—to the extent that it does not compromise proprietary information—should be a goal for both government and industry.

Notes on Terminology

The rapid pace of discovery related to nanomaterials and nanoscale processes is in some cases ahead of the systems of agreed-upon terminology and nomenclature for other materials used in research and manufacturing, which do not generally consider size as a criterion. For parties who are describing nanomaterials for the purposes of research or commerce, as well as for those who are responsible for establishing procedures and limits for safe use of engineered nanoscale materials, the creation of widely accepted terminology is essential.

For better understanding of terms used in this document, the following definitions are provided:

Engineered nanoscale materials, or nanomaterials, are those that have been purposefully manufactured or synthesized to have a size with at least one dimension in the range of approximately 1–100 nm and that exhibit unique properties determined by this size. *In this document, the term "nanomaterials" used alone will be shorthand for engineered nanoscale materials.*

The acronym "EHS" will be used in this document as shorthand for the collection of fields associated with the terms "environmental health, human health, animal health, and safety" when used in the context of risk assessment and risk management. While a variety of acronyms derived from permutations of the terms environment, health, and safety exist in the scientific and public health policy literature, "EHS" within this document has just one interpretation, as stated above.

RISK ASSESSMENT AND RISK MANAGEMENT

Many beneficial technologies and products have associated risks that are successfully managed, for example, electric power, medical X-rays, and gasoline. In general, risk of harmful effects attributable to chemicals, materials, or other products is a function of hazard and exposure in combination; that is, risk occurs only where the material is hazardous and exposure is quantitatively sufficient for biological response. Risk assessment is a process by which information is analyzed in a rational framework to determine the likelihood that a substance will cause harm to exposed persons or ecosystems (NRC, 1983). Risk assessments are conducted to provide the best possible scientific characterization of risks based on a rigorous analysis of available information and knowledge. In order to assess risk, it is necessary to identify and characterize possible hazards and to estimate the likelihood and magnitude of exposure.

Hazards can be defined as those materials or processes that produce toxic effects in humans or in the environment, or that have other potential adverse effects, such as causing fires or explosions. Hazards can be classified in terms of harm posed to living organisms—such as humans, wildlife, and vegetation—and ecosystems. In human health, hazards can be associated with transient biological response, such as irritation to the skin or eyes, or with serious systemic and persistent health effects such as organ impairment or failure. The characterization of hazards includes quantification of

toxicity through testing and determination of specific biological response as a result of interaction with a compound of interest. This approach is not unique to nanomaterials; many or most of these processes would be equally applicable to materials emerging from any new technology.

It is expected that exposure potential for some nanomaterials will be very limited to nonexistent, whereas exposure potential for other materials will exist at one or more stages of their product life cycles. Research on potential exposure must evaluate whether, and to what degree, exposure will occur for each nanomaterial at each stage of its life cycle. Characterization of exposure involves methods and tools for measuring materials in various media and organisms. One approach, an initial life cycle screening approach, may be useful to express the range of exposure likelihoods and potential areas of focus for research across the life cycle for products containing nanomaterials. For example, using a matrix approach, it would be possible to express the likelihood of exposure for key segments of the population (i.e., worker, consumer, patient, and the general public) across stages covering the life cycle of the nanomaterial from research and development to manufacture, distribution, use, and disposal (see Table 1 below). Each population segment/product stage combination then could be evaluated for exposure risks (e.g., inhalation, intravenous, dermal contact, eye exposure, and oral ingestion).

Table 1. Matrix for Tracking Exposure Potential and Life Cycle Information

Potential Recipient of Exposure	Product Life Cycle Stage				
	Research and Development	**Manufacture**	**Processing/ Distribution**	**Use**	**Disposal**
Worker	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:
Consumer	N/A	N/A	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:
Public (non-consumer)	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:	Inhalation: Oral: Dermal:
Environment	Water: Soil: Air:	Water: Soil: Air:	Water: Soil: Air:	Water: Soil: Air:	Water: Soil: Air:

This matrix shows one way of organizing exposure and life cycle information. The research needs at various stages of a product's life cycle and available research findings can be tracked by exposure route (e.g. oral, dermal, release in soil, release in air) and by the potential recipient of the exposure. The term workers here refers to those individuals who might be exposed to a nanomaterial or a product containing nanomaterials at the site of experimental research, manufacture, distribution, industrial use, or disposal. Consumers refers to those who might be exposed as a direct result of their choice to use a product in its commercial form. The non-consumer public, in contrast, might be indirectly (and often without choice) exposed to a product, usually at a site remote from where it was used. The environment, including air, water, soil, and biota (e.g. plants and wildlife) could be exposed to nanomaterials through intentional or unintentional releases. For some nanomaterials, the likelihood of exposure through various routes may change throughout the life cycle of the material and may differ across population segments. N/A = Not Applicable.

Hazard and exposure are linked by dosimetry—i.e., measurement of the amount of material in the body or the environment. Risk characterization, the last step in risk assessment and the starting point for risk management, includes a summary of key conclusions from the hazard, exposure, and dose components of the risk assessment and documentation of all supporting evidence. Risk characterization includes a description of the nature and likelihood of the risk, identification of individuals or groups at risk, the severity of the anticipated effects, the strength of the evidence supporting the conclusions of risk, uncertainty about the nature or magnitude of the risk, and other relevant factors, including range of expert opinion regarding key elements of the risk assessment and the relationship between effects caused by the exposure and background rates of those effects (Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997).

Risks posed by nanomaterials, like risks posed by chemicals, cannot be easily generalized. Both hazard and exposure potential will vary widely for different nanomaterials and for different products or applications that incorporate nanomaterials. However, further research may enable nanomaterials to be grouped according to certain structures and compositions and their potential for risk assessed as a group. In the meantime, risk assessments must be made in the face of considerable uncertainty and on a case-by-case basis. Tiered testing approaches to risk assessment that integrate both effects and exposure considerations for nanomaterials may be appropriate (Oberdörster et al., 2005a). Increasing computational capabilities could enable the modeling and possibly the prediction of biological responses to nanomaterials. Further, collaboration and multidisciplinary approaches may speed the development of knowledge for proper sample handling and processing.

Where nanomaterials are incorporated into products, such as computer circuit boards, the potential for exposure during use is unlikely because nanomaterials are effectively embedded in the product matrix. Although products containing embedded materials may have less risk for consumers, potential exposure of workers involved in the manufacture of such materials must still be considered, as should potential exposure of workers, the general public, or the environment during recycling or disposal at the end of product life. Predicting the risk of nanomaterials, therefore, includes conducting research, developing protocols, and gathering data to evaluate nanomaterial products over their lifetimes and assessing when, where, and how exposure to humans or ecosystems could occur.

Good risk assessment is essential for good risk management. Following identification of a risk, risk managers can evaluate options for addressing the risk and make informed decisions that reduce or avoid the risk. Among the options are replacing a hazardous material or process with a less hazardous one and using engineering controls to minimize exposures in the workplace. In the case of medical therapies, following specific protocols can minimize undesirable side effects in patients. Life cycle assessment studies may be used to identify opportunities for risk management through materials selection, product design, manufacturing process engineering, or recycling to reduce potential risks or adverse impacts at any of the stages. In some cases, use of nanomaterials may reduce the use of known hazardous materials.

FEDERAL NANOTECHNOLOGY EHS RESEARCH

The NNI has recognized the importance of environmental, health, and safety (EHS) research from its inception in 2001. Accordingly, the Federal Government supports research that will allow new products resulting from nanoscience to be introduced and used safely.

Government-funded basic and applied research toward understanding the EHS impacts of nanomaterials generally falls into three broad areas: (1) research to expand knowledge and further the understanding of how nanomaterials behave, (2) research to develop instrumentation and methods for

measuring, characterizing, and testing nanomaterials and for monitoring exposure; and (3) research contributing to safety assessments of nanomaterials and nanomaterial-based products.

During fiscal year 2003, the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the National Science and Technology Council (NSTC) Committee on Technology established the Nanotechnology Environmental and Health Implications (NEHI) Working Group to promote dialogue among the Federal agencies in the field of EHS research. In fiscal year 2005, the NEHI Working Group was formally chartered to

- provide for exchange of information among agencies that support nanotechnology research and those responsible for regulation and guidelines related to nanomaterials
- facilitate the identification, prioritization, and implementation of research and other activities required for the responsible development, utilization, and oversight of nanotechnology, including research methods for life cycle analysis
- promote communication of information related to research on environmental and health implications of nanotechnology to other government agencies and non-government parties

The NNI agencies have funded EHS research since 2001. In 2005, approximately $35 million was devoted to research whose primary purpose is to understand and address potential risks to health and the environment posed by this technology. The estimated investment in this research for 2006 is $38 million, and the President's 2007 budget request calls for increasing the amount to $44 million. Developing a fundamental body of knowledge, creating specialized research facilities, and sponsoring programs for education and training people in EHS research are essential elements of the NNI efforts in EHS. NSF has played a large role in all three of these areas of EHS research since the inception of the NNI. Due to the increased awareness that the understanding of nanomaterial toxicology and other related fields of study will improve only with more basic research and instrumentation and metrology development, NNI investment reports in the future will provide more detail about the funding in each of the areas covered in this document.

Top strategic priorities of the NNI agencies include support for research and development leading to a detailed understanding of the health and safety impacts of nanotechnology for researchers, workers, consumers, and the public and of the environmental impacts of various applications of nanotechnologies. For 2007, seven NNI agencies requested funding for such R&D, including National Institutes of Health (NIH), National Institute for Occupational Safety and Health (NIOSH), National Institute of Standards and Technology (NIST), Department of Defense (DOD), Environmental Protection Agency (EPA), National Science Foundation (NSF), and United States Department of Agriculture (USDA) Cooperative State Research, Education, and Extension Service (CSREES). All of these agencies and nine others participate in the NEHI Working Group.

Coordination of information related to risk assessment of nanotechnology products takes place through participation in the NEHI Working Group. In addition, numerous interagency collaborations on EHS research result from interaction through the NSET Subcommittee and the NEHI Working Group. Specifics of these collaborations can be found in the NNI Supplement to the President's 2007 Budget (see www.nano.gov/NNI_07Budget.pdf).

DOCUMENT DEVELOPMENT

The NEHI Working Group was created by the NSET Subcommittee in 2003 with the purpose, among other things, of facilitating the identification, prioritization, and implementation of research and other activities required for the responsible research, development, utilization, and oversight of nanotechnology. This document reflects the efforts of the NEHI Working Group to begin this

facilitation process and, specifically, to describe the EHS research and information needed to enable sound risk assessment and risk management.

The research needs were identified in a process that involved direct inputs from the Federal agencies that regulate and/or conduct research in nanotechnology and other inputs as described in the following sections. Input from the regulatory agencies was particularly important in that it identified research needs related to risk assessment and management of nanomaterials in view of the various regulatory authorities. As such, this document will be an integral part of the interagency process by which Federal nanotechnology EHS research is coordinated.

Also contributing greatly to the preparation of this document was early work by the NEHI Working Group on nanotechnology risk assessment issues. Expertise from working group members, along with input from other experts, was used to develop an influence diagram that described the main inputs needed to conduct nanomaterial risk assessments (Morgan, 2005). The influence diagrams describe the system of variables that experts hypothesized might influence hazard. Figure 1 below shows the top-level diagram. This decision diagram identifies potential areas of research that might be needed to understand whether, how, and to what degree these variables relate to hazard. The Morgan (2005) influence diagrams illustrate the complexity in this undertaking by showing the system of information that experts, including the NEHI Working Group members, hypothesized might be needed to conduct a risk assessment.

The five research areas described in Chapters 2–6 of this document reflect the general areas of research identified by the agencies as necessary for evaluating environmental, health, and safety issues for nanomaterials. *The order of the chapters in which these areas are presented is not intended to reflect prioritization*. Each chapter includes a brief description of the topic and its relevance to understanding EHS effects of nanotechnology, summaries of existing Federal research efforts, identification of primary needs for research and information, and, in most cases, suggestions for possible approaches that will build on current research and research directions.

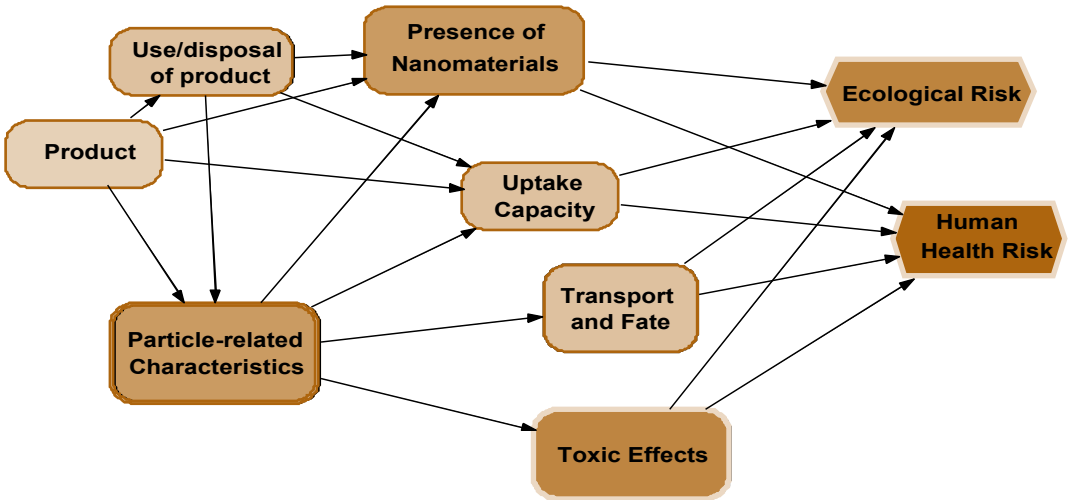

Figure 1. Influence Diagram for Nanomaterial Properties Relevant to Evaluation of Hazard. Each box in this figure represents a module that contains a system of variables. The detail contained within each module is shown in nested subdiagrams that are described in Morgan (2005). The rounded boxes are variables and the hexagon-shaped boxes are the areas of focus. The arrows indicate hypothesized influence, so that an arrow from variable 1 to variable 2 means that variable 1 is hypothesized to influence variable 2. All the variables have some hypothesized influence, either direct or indirect, on the focus areas (© 2005 Blackwell Publishing; reprinted by permission from Morgan, 2005).

Other Nanotechnology EHS Research Needs Documents

A number of reports have offered informed opinions regarding research needed to properly assess and manage nanotechnology-related risks and benefits to health and the environment. These reports—from a variety of stakeholders including government agencies, commercial entities, and academia—were reviewed in the preparation of this document. The rapid development of publications on this issue makes any such collection almost certainly incomplete. However, these documents are in general agreement that at least some nanomaterial applications pose potential risks and that research is needed to improve assessments of those risks and to enable appropriate risk management. Development of this document has been informed by many of those reports, which are listed in the references section of this publication.

A few resource documents deserve special attention in this discussion. One such document was developed by representatives from the chemical and semiconductor industries in consultation with Government agencies. Their report, *Joint NNI-Chemical Industry Consultative Board for Advancing Nanotechnology and Semiconductor Research Council CWG5: Nanotechnology Research Needs Recommendations* (Joint Chemical Industry Consultative Board for Advancing Nanotechnology, 2006), outlines those industries' priorities for government research in EHS related to nanotechnology.

Another publication of particular value in preparing this document was the Environmental Protection Agency (EPA) *Nanotechnology White Paper* (U.S. EPA, 2005), which was released in draft form for public comment in December 2005. This paper identifies and describes the issues that EPA must address to ensure protection of human health and the environment as this new technology is developed. The draft white paper addresses risk assessment and management issues and the agency's statutory mandates. It identifies research needs for both environmental applications and implications of nanotechnology and concludes with recommendations on next steps for addressing science policy issues and research needs.

Also providing valuable information for this document was the National Institute for Occupational Safety and Health (NIOSH) and its recent publications, including *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* (NIOSH, 2005a), a draft guidance and discussion document that outlines current knowledge about the occupational health and safety implications and applications of engineered nanoscale materials, using internal and external research data. This NIOSH document also offers interim recommendations on occupational safety and health practices in the production and use of nanomaterials, including mitigation of potential workplace exposures. These interim recommendations will be updated and revised as newer data become available. In addition, the *Strategic Plan for NIOSH Nanotechnology Research: Filling the Knowledge Gaps* describes a timely, multidimensional research agenda for NIOSH and its research partners to lead the occupational safety and health community collaboratively in nanotechnology research. (These and other NIOSH documents are available on the NIOSH nanotechnology website, www.cdc.gov/niosh/topics/nanotech/.)

Internationally, the white paper prepared by the Royal Society/Royal Academy of Engineering (RS, RAEng) in the United Kingdom, *Nanoscience and Nanotechnologies: Opportunities and Uncertainties*, provides a comprehensive look at emerging nanotechnologies, including benefits and potential risks (RS, RAEng, 2004). Noting that nanomaterials take many forms (e.g., spherical particles and tubes), the report addresses concerns over potential environmental and health risks of nanomaterials. Following the publication of the RS, RAEng report, the British government commissioned two studies to explore hazard and exposure data needs (Tran et al., 2005; Mark et

al., 2005). At the same time, the European Commission funded a separate study led by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to examine the efficacy of current risk assessment methodologies on nanomaterials (EC-SCENIHR, 2005). This report identifies eight research needs (or "critical knowledge gaps") requiring attention for risk assessment.

The research recommended in existing reports for scientifically based risk assessment varies in certain details but, in general, is well aligned. All of the reports reviewed for this document recognize that the greatest exposure potential to humans and the environment from nanomaterials would come from those that are "free" or not otherwise integrated as elements of larger materials. The reports stress the need for research in the following areas: nanomaterial characterization, methods for identifying hazards, understanding biological response to nanomaterials, and characterizing nanomaterial exposure and transport (in humans and the environment). In support of these efforts, the reports also call for common nomenclature to classify nanoscale particles and effectively communicate results. There is less agreement with respect to which research areas deserve highest priority (e.g., exposure vs. hazard identification). *This document identifies priority research, but does not prioritize within or among the research categories.*

THE PURPOSE OF THIS DOCUMENT

The primary purpose of this document is to identify for the Federal Government the environmental, health, and safety research and information needs related to understanding and managing the potential risks of engineered nanoscale materials that may be used in commercial or consumer products, medical treatments, environmental applications, and research.

This document will be used by the NSET Subcommittee and Federal agencies to inform and guide research programs. It also communicates to various non-government stakeholders approaches for obtaining the knowledge and understanding necessary to enable risk assessment and management of nanomaterials. Industry producers and users of nanomaterials, for example, may use this document to inform their own research, risk assessment, and risk management activities.

The Federal Government, through its agencies, implements various statutes and regulations to ensure that the risks of products are appropriately and adequately managed. Information regarding the risks and benefits of nanomaterials will be utilized by regulatory bodies that are responsible for protecting public health and the environment.

EHS research, which will increase the understanding of risks and benefits of nanomaterials, is supported by various stakeholders, including the U.S. Government, other governments, and industry. Federal funding of such research is intended to increase general understanding of risks and benefits of nanomaterials and to provide the scientific basis for regulatory decision making for materials and products. Federal funding also supports development of tools and methods for characterization and measurement that are fundamental to risk assessment and management. Manufacturers generally carry out research to determine safety of their products and in some cases are required to provide scientific data for regulatory decision making by the government.

By outlining the spectrum of research needs, the NNI agencies expect to accelerate progress toward comprehensive understanding of the risks and benefits for various types of nanomaterials. The knowledge gained from subsequent research will allow potential risks to be avoided or appropriately minimized during application and product development and to be managed where the advantages of specific materials make such steps worthwhile. The information also can lead to pollution prevention benefits where the potential risks and impacts of nanomaterials are less than those of conventional materials. This document addresses the NNI agencies' current best understanding of the research

and information needs for the assessment of EHS issues associated with *engineered nanoscale materials*, defined as nanomaterials that are intentionally designed and produced. This document does not directly address risk assessment of nanomaterials that occur *naturally* or are produced by physical or biological processes such as dust from deserts or from shell abrasion. The document also does not address nanoscale materials that are *incidental* byproducts, i.e., unintentionally produced from manufacturing or other processes such as welding or combustion. However, it is clear that the substantial body of knowledge related to exposures to these other categories of nanoscale materials (such as diesel exhaust, welding fumes, and ambient dusts) will inform risk assessment for engineered nanoscale materials (U.S. EPA, 2004 and 2006).

PRINCIPLES FOR IDENTIFYING AND PRIORITIZING EHS RESEARCH

At this early stage in the development of nanomaterials and their applications, it is useful to establish principles for identifying and prioritizing EHS research needs. Application of such principles allows for more efficient advancement in understanding the properties, behaviors, and potential risks of nanomaterials and more productive use of available resources. The NSET Subcommittee, through its NEHI Working Group, has created the following principles as guidelines to help researchers, program managers, and policy makers prioritize EHS research and investment.

1. Prioritize research based on the value of information. This is the overarching principle from which all of the subsequent principles flow. The value of any particular piece or set of data or information for assessing risks of a given nanomaterial depends directly on various factors including

- The extent to which the information will reduce uncertainty about benefits or risks. Key uncertainties need to be identified and evaluated in light of both the likelihood of health or environmental risk and the magnitude of benefit from a specific application. Similarly, reducing uncertainty for nanomaterials will enable safer manufacture, use, and disposal.
- The extent to which information can be expected to lead to broad knowledge about the properties and behavior of nanomaterials or classes of nanomaterials more generally. For example, certain computational tools may be especially powerful and cost effective in enabling materials to be designed to achieve the desired properties while reducing toxicity.
- The extent of use expected for the nanomaterial. It is necessary to identify for toxicological study—which is time consuming and costly—those nanomaterials that are likely to be used in multiple products or processes.
- The exposure potential for workers, consumers, or the environment to the nanomaterial being used in or developed for applications.
- The potential to leverage relevant existing data. In the case of nanoscale materials, there is an extensive body of existing research on incidental nanoscale materials—for example, diesel exhaust—that will inform the identification and prioritization of research and information needs for nanomaterials. (In turn, research results for nanomaterials will aid in understanding the sometimes more complex problems due to variability in size and composition for incidental and naturally occurring nanoscale materials.)

In the broad area of applications development, research that integrates toxicological or risk assessment of nanomaterials as part of their design or engineering would be extremely valuable and would increase the likelihood of producing materials that are environmentally and biologically compatible.

2. Leverage international and private sector research efforts. Although the United States is a world leader in nanotechnology R&D, approximately 75 percent of the research investment worldwide is

provided by other nations or regions. Moreover, the total R&D spending by the private sector on nanotechnology is now estimated to equal or exceed the combined government investment. It is not surprising, therefore, that the need for EHS research related to nanotechnology is a global concern. Research directed at understanding EHS issues benefits nations that produce nanotechnology-enabled products, as well as those who use them. Redundancy in research can be avoided and resources used more effectively through cooperative efforts at the international level. Resources can be leveraged through joint calls for proposals, workshops, data sharing, bilateral engagement, and other international activities, such as those of the Organisation for Economic Co-operation and Development (OECD) and the International Dialogue for the Responsible Research and Development of Nanotechnology (co-sponsored by NSF and several other international governmental bodies).

3. Use adaptive management for nanomaterial EHS research. New developments in nanomaterials are advancing rapidly and can be expected to continue to do so in the coming years. In order to expedite development of information that enables both protection and beneficial applications for human health and the environment, it is important to adapt research strategies in accordance with emerging R&D directions. Agency funding decisions for EHS research should be similarly flexible to avoid missed opportunities and to remain focused on research with the greatest value.

NEXT STEPS

In order to expedite progress toward addressing the research needs described in this document and to adjust those needs as development, understanding, and use of nanomaterials advance, the NSET Subcommittee—in part through the efforts of the Nanotechnology Environmental and Health Implications (NEHI) Working Group—will work with the NNI agencies to

- Establish research priorities. Priorities will be evaluated further, based primarily on the principles outlined above. Other factors that will be considered include the time frame for developing the information—because certain studies are inherently lengthy—and the availability of research tools.
- Evaluate in greater detail the current NNI EHS research portfolio.
- Perform a "gap analysis" of the NNI EHS research compared to the prioritized needs.
- Coordinate and facilitate among the NNI agencies' research programs to address priorities. Agencies will work individually and jointly, where possible, to address research needs.
- Establish a process for periodic review of progress and for updating the research needs and priorities. Such a review must take into consideration advances made by entities other than U.S. Government-funded bodies, such as advances by the private sector and other governments.

Given the number of entities that will contribute to knowledge about nanomaterials and their impacts, collaboration among the various research groups is important. Furthermore, discourse among the multiple stakeholders with various interests will be valuable, especially with regard to strategic and interim goals for filling the EHS information gaps for nanomaterials. The NSET Subcommittee and NNI member agencies plan to make the priority-setting process a dynamic, open, and transparent process. Input from citizen and industry groups, academia, and other research entities will be gained through workshops, public hearings, and other means. Input will be carefully considered when establishing research priorities.

2. Instrumentation, Metrology, and Analytical Methods

This area identifies research to enable new instrumentation and standard measurement protocols, as well as the development of reference materials and data related to the detection, characterization, and measurement of physical, chemical, and biological properties of engineered nanoscale materials in environmental and biological matrices (e.g., air, water, soil, cells, tissues, organs, organ systems, and whole organisms). Also addressed is the development of terminology, nomenclature, and standards for engineered nanoscale materials, a cross-cutting need for each research area discussed in this document.

TERMINOLOGY, NOMENCLATURE, AND STANDARDS DEVELOPMENT FOR ENGINEERED NANOSCALE MATERIALS

Basic terminology and a comprehensive nomenclature or taxonomy for nanomaterials have not yet been developed, but development efforts are under way. Such terminology and nomenclature would enable nanomaterials or products that contain nanomaterials to be identified unambiguously across government(s), industry, and academia. Standardized language would facilitate effective communication among researchers and support the development of regulatory definitions applicable to nanomaterials. Also under way is standards development for instrumentation and metrology to characterize the properties of nanomaterials, as well as to measure and control exposures to nanomaterials. These standards will improve toxicology and scientific research, in general, as well as facilitate confidence in product consistency in commerce.

Selected Relevant Federal Government Actions

- Scientists from several Federal agencies as well as the NNI's National Nanotechnology Coordination Office (NNCO) are working on developing standards for nanotechnology-related terminology and nomenclature; measurement and characterization of nanomaterials; and environmental, health, and safety aspects of nanotechnology. NNI agencies are contributing to the work of U.S.-domiciled standards development organizations (including ASTM International, the Institute of Electrical and Electronics Engineers, and the National Electrical Manufacturer's Association) to develop voluntary, consensus-based nanotechnology standards for international use.
- In June 2004, the American National Standards Institute (ANSI) established a Nanotechnology Standards Panel to facilitate and coordinate U. S. efforts in nanotechnology standards development. Subsequently, the International Organization for Standardization (ISO) established a Technical Committee (ISO TC 229) for nanotechnologies. ANSI then accredited a Technical Advisory Group (ANSI-TAG) to represent the United States on the ISO Technical Committee. One of the working groups of ISO TC 229 is focused on developing terminology and nomenclature for nanotechnology, as is its parallel in the ANSI-TAG.
- The United States leads the ISO TC 229 Working Group on Health, Safety, and Environmental Aspects of Nanotechnologies. At its June 2006 meeting, ISO TC 229 approved a U.S. submission of a new work item proposal to develop an ISO Technical Report on Current Safe Practices in Occupational Settings Relevant to Nanotechnologies. The NIOSH document *Approaches to Safe Nanotechnology*: *An Information Exchange with NIOSH* will serve as a benchmark for that report.

- A second ISO TC 229 Working Group on Metrology and Characterization is developing standards for a minimum set of measurement methods for characterizing both single-wall and multiple-wall carbon nanotube materials for purity and types of contaminants—an important step both for improving consistency in conducting research on the potential toxicity of these engineered nanoscale materials and for advancing trade in these materials.
- ANSI is working with ASTM International, which under its E56 Committee on Nanotechnology has established a number of technical subcommittees: E56.01, Terminology and Nomenclature to develop and harmonize definitions of nanotechnology-related terms; E56.02, Characterization; E56.03, Environment, Health and Safety; E56.04, International Law & Intellectual Property; and E56.05, Liaison & International Cooperation. The first standard, E2456-06 Standard Terminology for Nanotechnology, was approved in July 2006. In addition, three standards on biological testing of engineered nanoscale materials and four standards on engineered nanoscale materials characterization and sample preparation are in draft status.
- ASTM International has formed a partnership to work jointly with IEEE, the American Society of Mechanical Engineers, Semiconductor Equipment Manufacturers International, American Institute of Chemical Engineers, and NSF International (formerly the National Sanitation Foundation) to develop global nanotechnology terminology standards. Several Federal agencies participate in one or more of these standards development organizations.

Research/Information Needs

Develop useful approaches to identify and categorize nanomaterials by size, composition, and morphology. General terminology is lacking for nanoscience and technology, including definitions and systematic terminology for material size, composition, and morphology.

Defining a common language for describing unique nanoscale phenomena and for sharing health and environmental effects research on nanomaterials is challenging. To understand and compare research results, a minimum set of physicochemical characteristics of materials used in biological effect studies and fate/exposure studies must be selected and a common language for describing the materials and characteristics must be developled.

Possible Research Approaches

Research that contributes to an internationally recognized system of terminology and nomenclature for nanomaterials will be most valuable.

A useful set of physicochemical characteristics may be modeled after the "minimum information about a microarray experiment" (MIAME) standards that evolved for microarray analysis (www.mged.org/Workgroups/MIAME/miame.html). Such targeting not only assists comparison of study results but also reduces inadvertent variation that contributes to confusion for extrapolations across studies.

Issues to consider in developing common language for nanomaterials EHS research include processes for data sharing, data provenance, analytical platforms, and ontologies. Ontologies use *object models* describing the relationships between words to query and extract data. This allows users from disparate scientific fields to mine databases using their own discipline's familiar keywords rather than requiring all parties to agree on a common data dictionary.

ANALYTICAL TOOLS AND METHODS

Evaluating the effects of nanomaterials on the environment and human health may require considerable knowledge of the nature and properties of the nanomaterials, including such characteristics as purity, particle size and distribution, shape, crystal structure, composition, surface area, surface chemistry, surface charge, surface activity, and porosity. A broad array of analytical tools and methods are needed to perform such characterizations, among them a wide variety of optical, microscopic, spectroscopic, chromatographic, and nuclear methods. In many cases further development of existing tools or the creation of new instruments or approaches will be necessary to obtain reliable and reproducible information for engineered nanoscale materials. This underlying information is critical in making associations between specific nanomaterials, particular behavior, and resulting effects. The key to these tools and approaches is *metrology*, the science of measurement. Research on instrument development is a cross-cutting need that affects many of the other research needs identified in this document.

Furthermore, there is currently a lack of generally accepted, acknowledged, and/or validated measurement methods, reference data, and standards for the determination of the nature and properties of engineered nanoscale materials. For example, representative reference species from broad classes of nanomaterials have not been established, yet these are necessary to develop metrology for measuring, testing, and characterizing materials in a wide range of biological and environmental media. Both the pure forms of the materials and the materials in altered states (such as in solution) require consideration. The relative lack of basic scientific information in this area poses significant challenges both for developing new materials and for regulatory review.

Selected Relevant Federal Government Actions

- The National Institute of Standards and Technology (NIST) supports development of methods to characterize and validate performance of conventional instrumentation, development of Standard Reference Materials, and research to develop new analytical methods and measurement technology. NIST also operates specialized nanotechnology facilities including the new Center for Nanoscale Science and Technology. These facilities provide access to a wide range of optical, mechanical, electrical, and magnetic measurement techniques for dimensional characterization and determination of material and mechanical properties at the macroscale, microscale, and nanoscale.
  - Topical research areas at NIST include fundamental science and measurement techniques, characterization of materials, development of nanoscale electronics, nanochemistry, and nanobiotechnology methods, and quantum computing and communications. NIST-wide nanotechnology research also focuses on the miniaturization of analytical techniques for the detection or characterization of matter such as the development of cantilever and "lab-on-a-chip" devices for sensing, detection, and separation of matter traceable to the International System of Units (SI) units. (More information on these activities is available at www.cstl.nist.gov/nist839/839.04/microfluidics.html and www.ceramics.nist.gov/ftproot/AR2005_Ceramics.pdf.)
  - Other NIST nanotechnology research activities include the development of micro-fabricated atomic frequency references and calibration services for force and torque at the nanonewton level. Funded metrology programs include Fundamental Metrology for Carbon Nanotube Science and Technology, Metrology for the Fate of Nanoparticles in Biosystems, and Bio-Imaging: A 21st Century Toolbox for Medical Technology.

  - Recent NIST workshops have included topics such as standardizing nanotube measurement, analysis, and reporting protocols for single-wall carbon nanotubes; measurement and standards needs in nanobiotechnology; and challenges associated with the characterization of particles (including those at the nanoscale) with sessions on sample preparation, statistical experimental design, and established and emerging measurement techniques.
  - In 2004 NIST opened a unique nanomaterial science research facility, the Advanced Measurement Laboratory (AML). The AML is designed to assist U.S. industry, university, and government partners with new high-accuracy measurement technologies, databases on the fundamental properties of nanomaterials, and other supporting tools and capabilities to promote advances in nanomaterial science.
  - In 2006, NIST established the Center for Nanoscale Science and Technology. The Center will contribute to progress in the NNI program component areas with emphasis on instrumentation research, metrology, and standards for furthering the development of tools and standards needed to advance research and to build technical infrastructure supporting the manufacture and commercialization of nanoscale materials, structures, devices, and systems (see cnst.nist.gov).
  - As part of the Center for Nanoscale Science and Technology, NIST established a nanofabrication facility that provides state-of-the-art ultraclean facilities for the fabrication of nanoscale devices, structures, Standard Reference Materials, microelectromechanical systems (MEMS), and bio-devices. It also provides access to a wide variety of measurement and characterization tools, technologies, and expertise to NIST and its partners.
  - Products, standards, and technologies developed as part of these NIST-wide nanometrology research and development programs will support metrology needs for nanomaterials and related environmental health and safety efforts.
  - Standard Reference Materials are being developed for the physical and chemical characterization of nanomaterials, including a suite of gold nanomaterials with diameters in the range of 1–100 nm for calibration of instruments and measurements; physical *in vitro* and *in vivo* characterization studies in collaboration with the Nanotechnology Characterization Laboratory (NCL) at the National Cancer Institute (NCI); elemental Standard Reference Materials (thin films, single-phase nanoscale particles, and more complex systems) for electron and ion beam analytical imaging instruments; NIST Reference Material 8475 Carbon Nanotubes; and particle-size standards in the nanometer to micrometer range for evaluating and calibrating specific types of particle-size measuring instruments such as optical and scanning electron microscopes and light-scattering instruments.

- The Nanotechnology Characterization Laboratory (NCL) at the National Cancer Institute (NCI) conducts preclinical tests of the efficacy and toxicity of nanoscale particles intended for cancer therapeutics and diagnostics (see ncl.cancer.gov).
  - The NCL characterizes physical attributes of nanoscale particles, *in vitro* biological properties, and *in vivo* compatibility using animal models.
  - The NCL assists the bio-nanotechnology community in identifying relationships between the physical structure of nanomaterials and their biomedical activity relevant to nanomaterial safety and efficacy.
  - The activities within the NCL represent a formal scientific partnership of the NCI with the U.S. Food and Drug Administration (FDA) and NIST.

  - The NCL has initiated a program for characterizing and cataloguing physical and biological properties of engineered nanomaterials used in cancer diagnosis and treatment.
  - The NCL is creating an informatics grid in which information will be made available relevant to the development of nanoscale drug delivery vehicles and structure activity relationships contributing to biocompatibility and toxicity (see nano.cancer.gov/about_alliance/nanotech_characterization_lab.asp).
- The Department of Energy (DOE) is establishing and operating five Nanoscale Science Research Centers (NSRCs) as user facilities (see nano.energy.gov).
  - Access to the NSRCs is open to all and based on merit review of submitted proposals, making comprehensive suites of state-of-the-art equipment and corresponding expertise available to the scientific community.
  - The NSRCs are located close or adjacent to other major user facilities for X-ray, neutron, and electron scattering, and provide gateways to these powerful existing capabilities.
  - The NSRCs also participate in the development of new tools for nanoscale characterization and analysis, including synchrotron beamlines with unprecedented spatial resolution for imaging, modular microlaboratories for facilitating measurements on nanomaterials and improving their comparability, and cantilever and "lab-on-a-chip" devices for sensing, detection, and separation.
- DOE efforts in the area of novel and improved analytical tools and methods for nanomaterials include the Transmission Electron Aberration-corrected Microscope (TEAM) project, a multiyear development effort to create the basic platform for the next generation of transmission electron microscopes. Involving five electron scattering groups supported by DOE, as well as several commercial partners, the project re-envisions the instrument from the ground up in order to maximize its capabilities, building on recent advances in compensating for electromagnetic lens imperfections. Thus, the instrument being developed will include an advanced and more stable column, an improved electron source, novel sample-insertion and sample-handling mechanisms, novel correctors for several levels of aberration both in the probe-forming and image-forming lenses, and other improvements to allow unprecedented resolution, tomographic imaging at the atomic scale, and additional flexibility for spectroscopic and other analyses. (Further information on the TEAM Project is available at ncem.lbl.gov/team3.htm.)
- DOE is also supporting the development of other novel hardware and software for nanomaterial analysis, including instruments and detectors for neutron-scattering research at the Spallation Neutron Source.
- NIOSH has developed a web-based Nanoparticle Information Library to help occupational health professionals, industrial users, worker groups, and researchers organize and share information on nanomaterials, including their health- and safety-associated properties (see www2a.cdc.gov/niosh-nil).
- The NSF supports R&D through universities, research laboratories, and small businesses to create new tools needed to advance nanotechnology research and commercialization, including next-generation instrumentation for characterization, measurement, synthesis, and design of materials, structures, devices, and systems. (More information is available at www.nsf.gov/nano.) Large experimental facilities have been funded through NSF's Major Research Instrumentation program. The largest contribution for new instrumentation is provided through single-investigator and small-group projects.

- NSF supports work on analytical tools and methods development through several user networks and university-based centers: the National Nanotechnology Infrastructure Network (NNIN), an integrated partnership of 13 user facilities, of which two are focused on characterization of nanoscale particles; a group of 16 Nanoscale Science and Engineering Centers, of which one is focused on novel instrumentation; a center on environmental aspects of nanomaterials; four centers on nanomanufacturing processes and tools; a network of six Materials Research Science and Engineering Centers; an Engineering Research Center focused on nanoscale measurements; and a Science and Technology Center focused on nanobiotechnology processes and tools. The NNIN network provides extensive support in nanoscale fabrication, synthesis, characterization, modeling, design, computation, and training in an open, hands-on environment available to all qualified users. NSF also supports analytical work through the Network for Computational Nanotechnology, whose mission is to connect theory, experiment, and computation in the field of nanotechnology.
- The Department of Defense (DOD), via the Defense University Research Instrumentation Program and other programs, provides DOD facilities and research to support the development of new instrumentation for nanoscience research.

Research/Information Needs

Develop methods for detecting nanomaterials in biological matrices, the environment, and the workplace. Analytical methods for identifying and measuring the critical parameters related to nanomaterials in biological systems, the environment, and the workplace are not well-developed or readily available. As a result, these important metrics are infrequently or inaccurately reported. Further development of these methods is critical to nanotechnology EHS research. Accurate and validated reference materials and/or protocols also are needed to define the limitations and specificities of each analytical method for the analysis of biological, environmental, and workplace samples (Roberts et al., 2006). Additionally, methods for detecting and measuring the effects of nanomaterials (i.e., absorbed and effective dose) in biological, environmental, and workplace samples are in their infancy and must be developed (see Chapter 3, Nanomaterials and Human Health; Chapter 4, Nanomaterials and the Environment; and Chapter 5, Health and Environmental Surveillance).

Understand heterogeneity in nanomaterials. The relationship of batch-to-batch variation in nanomaterial production and biological activity or toxicity is not understood at this time. This potential variation can affect the assessments of expected toxicity for materials in use. Purity assessments; particle size, shape, and structure analyses; and the determination of chemical composition of nanomaterials will assist with understanding the heterogeneity in nanomaterials.

Understand the effect of modifications on the properties of nanomaterials. In the development of products, nanomaterials may undergo any number of modifications. These modifications may include coatings to reduce oxidation, addition of molecular groups to induce or diminish biological activity, or functionalizing them to enable their integration into final products. These modifications may affect the degradation of particles, their uptake by biological matrices, or the methods necessary to detect the presence of nanomaterials in human and environmental contexts.

Develop methods for assessing purity of materials. A variety of optical, microscopic, nuclear, chromatographic, and spectroscopic methods exist for assessing the purity of a material. Modifications or enhancements to these methods may be necessary, however, to apply them to nanomaterials. Validated measurement methods do not exist to assess purity of nanomaterials or to compare manufactured materials produced by different vendors or laboratories.

Develop methods for standardizing assessment of particle size and size distribution. Rapid, statistically valid, standardized methods are lacking for measuring both the size and particle-size distributions of nanomaterials. Automated microscopic methods for the rapid analysis and screening of a large number of nanomaterials would greatly facilitate the acquisition of knowledge about properties of nanomaterials. Methods for determining the sizes of particles smaller than 5 nm are especially inadequate. It may be helpful to explore correlations of electron microscopy with other size-measurement techniques, such as differential light scattering, in an effort to provide new mechanisms for researchers to evaluate the quality and comparability of measurements of particle size and particle-size distributions in the nanoscale regime.

Develop methods and standardized tools for assessing nanomaterial shape, structure, and surface area. Determining shape, structure, and surface area with nanometer precision is a challenge using current methods and tools. In general, conventional electron microscopy is not fast enough to provide population statistics adequate to characterize the structure of nanoscale engineered materials. A clear need is the capability for resolution on the atomic scale, and such capabilities are fundamental to primary calibration methods. A possible strategy for the determination of nanomaterial shape and structure is aberration-corrected analytical electron microscopy. Ion mobility mass spectrometry has not been thoroughly explored but may be an appropriate method for determining aggregation of nanomaterials. Surface areas may be determined using BET (Brunauer-Emmett-Teller) techniques, though this classical approach of using gas molecules as "rulers" likely needs to be modified for accurate characterization of nanoscale engineered materials.

Develop methods to characterize a nanomaterial's spatio-chemical composition. At the nanoscale, where single defects and slight changes to surface dimension and composition can dramatically influence reactivity, proper characterization of spatial composition is critical. Most chemical analytical techniques are designed for bulk materials and lack the spatio-chemical resolution to resolve differences in composition at the nanoscale. Three-dimensional chemical characterization of nanomaterials at the 1 nm resolution level is necessary for accurate assessment of the chemical composition of nanomaterials. Applicable techniques may include secondary ion mass spectrometry, X-ray photoelectron spectroscopy, Auger electron spectroscopy, analytical electron microscopy, and X-ray microanalysis.

Develop an inventory of nanomaterials and their uses. National and international tracking and monitoring of the production and use of nanomaterials are limited, and current production levels of nanomaterials are not well known. There is little information on companies currently in production mode or their industry sectors. Patterns and trends in production and use of products have not been comprehensively examined, and there is a paucity of data on trends (or projections) of growth. An inventory of materials and uses would assist in tracking and monitoring the production and use of nanomaterials. The value and cost of including in the inventory specific kinds of descriptive information and levels of detail should be considered.

The inventory could be used to examine patterns and trends in engineered nanomaterial production and use, including identification of industry sectors and specific establishments producing nanomaterials or products that contain nanomaterials.

Possible Research Approaches

A national program involving the Federal Government, industry, and academia could be established for characterization of nanomaterials. Such a broad-based program would help greatly with the analysis of nanomaterials in both pure and more complex forms, such as in solution or in biological

or environmental matrices. The initial foci of such efforts could be evaluating purity, size and distribution, shape, structure, spatial-chemical composition, and surface activity.

There is a lack of atomic-scale or molecular-scale modeling for nanomaterials. Coordination among practitioners of analytical science and of biological science will enable the modeling and possibly the prediction of biological interactions of nanomaterials. Collaborative or multidisciplinary approaches may speed the development of knowledge for proper sample handling and processing. Such approaches could provide fundamental insight into the physical and chemical properties of nanomaterials.

Other specific approaches for consideration include development of

- Standard Reference Materials for the chemical and physical characterization of nanomaterials
- global-scale, inter-laboratory, comparative exercises for characterizing nanoscale engineered materials at national metrological institute levels
- a program to accredit laboratories that characterize nanomaterials
- nationally recognized standard protocols for sampling methods necessary to determine individual exposure to nanomaterials in the workplace (see also Chapter 5, Health and Environmental Surveillance)
- nationally recognized standard protocols for sampling methods necessary to determine biomarkers indicative of biological exposure to nanomaterials (see also Chapter 5, Health and Environmental Surveillance)
- nationally recognized standard protocols for determining the concentration of nanomaterials in environmental media such as air, water, soil, food, and biota (see also Chapter 3, Nanomaterials and Human Health)
- a database and mathematical modeling structure that facilitate estimation of the biological or environmental response of a nanomaterial to changes in a defined set of physical parameters (see also Chapter 4, Nanomaterials and the Environment)

3. Nanomaterials and Human Health

This area addresses research on the biological response to engineered nanoscale materials and their byproducts, the results of which may contribute to identifying potential adverse health effects in humans. This includes research on subcellular components, cells, tissues, organs, organ systems, and whole organisms to determine biocompatibility and toxicity of various engineered nanoscale materials; and research to evaluate current toxicity screening tests and develop new tests as needed.

Size, shape, and surface chemistry are among key properties central to the utility of nanomaterials. These properties also fundamentally influence the way these materials interact within the human body. Understanding how the various characteristics of nanomaterials affect their biocompatibility and toxicity will support development of safer nanomaterials and nanotechnology products. Development of well-integrated, multidisciplinary research teams is critical to enable these studies.

One example of the roles nanomaterial properties play is how changes to surface chemistry can affect the biocompatibility and toxicity of particular nanomaterials. Positively charged nanoscale lipid vesicles (nanovesicles) induce cerebral edema, but neutral and low concentrations of negatively charged nanovesicles do not (Lockman et al., 2004). Studies have shown that modifying the surface of nanomaterials with surfactants or biocompatible polymers (e.g., polyethylene glycol) reduces the toxicity *in vitro* (Derfus et al., 2004) and alters the half-life and tissue deposition *in vivo* (Ballou et al., 2004). Such findings are relevant to drug delivery, for understanding the potential distribution of nanomaterials in the body, and for evaluating biocompatibility and toxicity. However, these material-specific and are difficult, at present, to extend to broad categories or classes of materials.

Nanoscale materials similarly may vary in their ability to be introduced into and circulated through the body. For example, one study discovered ultrafine carbon transport from the olfactory mucosa in nasal passages, via the olfactory nerve, to the olfactory bulb inside the blood-brain barrier (Oberdörster et al., 2004). Other studies have demonstrated that semiconducting quantum dots translocate to local lymph nodes in animals following intradermal or footpad injections (Kim et al., 2004; Roberts et al., 2005) or following topical application to dermabraded skin (Gopee et al., 2006).

Seemingly more so than at larger scales, the shapes of nanomaterials have interesting implications for biocompatibility. Current manufacturing technologies with atom-by-atom assembly of nanomaterials under highly controlled conditions enable synthesis of materials having different shapes but the same chemical composition. Studies of zinc oxide (ZnO) nanomaterials suggest that changes in shape alone (e.g., particles, cages, and "belts") influence physicochemical properties (Wang et al., 2004), which in turn can influence biological activity.

BIOLOGICAL RESPONSE

Homeostasis describes the totality of the physiological pathways and mechanisms that keep the body within the functional parameters defined as good health. Environmental exposures shift those parameters. The body's ability to minimize the impact of an exposure and maintain homeostasis distinguishes biocompatibility from toxicity. Sentinel mechanisms designed to maintain homeostasis include the antioxidant pathways, inflammation, and immunity. The magnitude of the protective response is generally proportional to the magnitude, complexity, and duration of the exposure, but elevated biological response or persistence of the exposure could lead to tissue injury and chronic adverse health effects.

Physiological response to nanomaterials is complex and influenced by physicochemical properties such as size and composition, purity of material following synthesis, type and degree of surface modifications, the inclusion of a surfactant or vehicle, the binding of biological molecules to the material following exposure, and the types of cells and organs exposed and degradation characteristics. Moreover, route of exposure as well as genetic, life status, and susceptibility factors may affect physiological response. Status factors including age, sex, or socioeconomic status may influence susceptibility to an exposure. Nanomaterials research, although in its infancy, has begun to provide clues about nanomaterial interaction with human physiology. Extensive existing scientific literature on ultrafine and fine particles and fibers has contributed greatly to understanding the physical and biological properties of these materials and provides a scientific basis for developing hypotheses for testing engineered nanomaterials.

The need for specific studies on the biological response to nanomaterials highlights another research challenge: the limited availability of well-characterized materials in sufficient quantity. Consequently, most current research is performed *in vitro*, not *in vivo*, and assesses acute exposure, not chronic exposure. Novel biological response, when identified, may necessitate development of new test methods to evaluate novel behavior of nanomaterials *in vivo*, and new *in vitro* tests to predict novel *in vivo* behavior. Moreover, although results have shown the utility of studies *in vitro* to compare relative toxicities of specific nanomaterials (Hussain et al., 2005), standardized dosing protocols have yet to be established for the testing of such materials *in vitro*.

Additionally, modifications to the surfaces of nanomaterials can alter biochemical reactivity and should be reflected in calculations of absorbed and effective dose. Processes that may modify nanomaterial surfaces include intentional or inadvertent chemical changes that may occur through sonication, grinding, or suspension in a vehicle in preparation for administration to a subject. Coatings may be applied before administration or may spontaneously develop during and after administration. Any surface modification has the potential to strongly influence the material's reactivity. Physicochemical characterization of nanomaterials following preparation and administration is required to understand the dose-response behavior of nanomaterials in biological systems.

Selected Relevant Federal Government Actions

- NIH's NCI has initiated a program at the Nanotechnology Characterization Laboratory for characterizing and cataloguing physical and biological properties of nanomaterials used in cancer diagnosis and treatment (see ncl.cancer.gov). The program is working to standardize approaches to characterize nanomaterials through physical, *in vitro*, and *in vivo* assays. The NCL, a partnership of NCI with NIST and FDA, will track and measure health effects related to nanotechnology, including EHS. NCL is developing standard protocols for physical characterization, *in vitro* mechanisms of toxicity, and identifying parenteral absorption, distribution, metabolism, elimination and toxicology (ADME/Tox) profiles of nanomaterials intended for medical applications. This knowledge can serve to inform environmental toxicologists about toxic mechanisms, target organs, and systemic clearance mechanisms for nanomaterials. Data resulting from NCL assays will help inform the nanotechnology community as it makes assessments of the overall risks involved in the manufacture, use, and disposal of nanomaterials.
- The National Institute of Environmental Health Sciences (NIEHS) has developed a trans-NIH and interagency Funding Opportunity Announcement to support research to investigate the biocompatibility and toxicity of industrial nanomaterials in mammalian systems. Six NIH institutes are partnering with the National Institute for Occupational Safety and Health and the Environmental Protection Agency.

- The National Toxicology Program (NTP), a partnership among NIEHS/NIH, NIOSH/CDC, and FDA, has developed a Nanotechnology Safety Initiative (ntp.niehs.nih.gov/go/nanotech) that focuses on three areas of research with respect to specific groups of nanoscale materials. Results from these NTP studies are anticipated to be available in the next 1–5 years, depending on the type of study. Longer-term rodent studies are also likely to take several years. The three NTP nanomaterials research areas are as follows:
  1. non-medical, commercially relevant and available nanoscale materials to which humans are being exposed (e.g., cosmetics)
  2. representative nanoscale materials from specific classes (e.g., fullerenes and metal oxides) so that information can be extrapolated to other members of those classes
  3. subsets of nanoscale materials to test specific hypotheses about key physicochemical parameters (e.g., size, composition, shape, or surface chemistry) that might be related to biological activity

  For all three of these areas, research activities are focusing initially on four classes of nanoscale materials:
  1. metal oxides (e.g., TiO_2 and ZnO), in collaboration with the Food and Drug Administration's National Center for Toxicological Research (NCTR)
  2. fluorescent crystalline semiconductors (quantum dots, in collaboration with NCTR)
  3. fullerenes (in collaboration with NIEHS)
  4. carbon nanotubes (in collaboration with NIOSH)
- NIOSH has established the Nanotechnology Research Center, which provides national and world leadership for research into the implications of nanoscale materials for work-related injury and illness. As part of its nanoscale material research program, NIOSH conducts toxicology studies of selected occupationally relevant nanomaterials (carbon nanotubes and metal oxides) for pulmonary, cardiovascular, and dermal effects.
- In 2003 EPA began to support research to address health, ecological, and environmental implications of nanotechnology through its Science to Achieve Results (STAR) grants program. In 2005 and 2006, EPA's STAR program partnered with NIOSH, NSF, and NIEHS in funding grants to examine the health and ecological effects of various classes of nanomaterials such as carbon-based materials, metal-based materials, and dendrimers. These grants examine a range of toxic endpoints of nanomaterials in the body (cellular cytotoxicity, gastrointestinal toxicity, pulmonary toxicity, and genotoxicity) and ecotoxicity (terrestrial and aquatic) for various classes of nanomaterials (see es.epa.gov/ncer/nano/research/index.html). EPA's Nanotechnology White Paper (U.S. EPA, 2005) identifies research needs that will lead to a strategy to complement, enhance, and integrate EPA's intramural and extramural health and ecological effects research in order to meet its mission and needs in the areas of environmental, health, and ecological implications of nanomaterials. These include comprehensive *in vivo* toxicity assessments of nanomaterials before and after interactions with environmental media associated with their applications, validated toxicity test methods, hazard identification, identification of susceptibility factors, mechanism(s) of injury and mode(s) of action, and development of models to predict nanomaterial toxicity.
- The Department of Defense supports research to enable physicochemical characterization of nanomaterials and associated toxicology assessments in marine, aeronautical, terrestrial, and space environments. This research includes developing approaches to assess, avoid, and abate adverse health (or environmental) impacts from defense utilization of nanomaterials.

- The National Science Foundation (NSF) supports fundamental research (except for clinical testing) on EHS implications of nanotechnology. NSF-funded basic research related to nanomaterials and human health involves all the NSF research directorates and addresses natural, incidental, and manufactured nanoparticles and nanostructured materials in the air, water, soil, biosystems, and working environments. Four NSF Nanoscale Science and Engineering Centers are investigating the safety of manufacturing nanoparticles: (1) Rice University (evolution of manufacturing nanoparticles in the wet environment); (2) Northeastern University (occupational safety during nanomanufacturing); (3) University of Pennsylvania (interaction between nanomaterials and cells); and (4) University of Wisconsin, Madison (EHS effects of nanostructured polymers). NSF's National Nanotechnology Infrastructure Network includes centers at two of its 13 major nodes (University of Minnesota and Arizona State University) with a focus on nanoparticle characterization.
- NSF has also funded about 20 interdisciplinary research teams (NIRTs) in areas related to basic understanding of nanomaterials and human health. Three examples are as follows:
  1. *Reverse Engineering Cellular Pathways from Human Cells Exposed to Nanomaterials.* This research is yielding results suggesting that single-wall nanotubes are relatively nontoxic (comparable to silica) to primary human cells (skin, lung).
  2. *Biocompatible Nanoparticles for Probing Living Cellular Functions and Their Potential Environmental Impacts.* In this project a team of biologists, engineers, and chemists are designing biocompatible nanoparticles for sensing and measuring in real time transport mechanisms in cell membranes. The study will lead to new knowledge on transport of nanoparticles through protein membranes and on design and assembly of molecular pumps and sensors.
  3. *Understanding Robust Large Scale Manufacturing of Nanoparticles and Their Toxicology.* This project involves partnership between academia, government, and industry, as well as the disciplines of chemistry, chemical and mechanical engineering, and medicine. The study is employing a specialized reactor to generate engineered nanoparticles in collaboration with Cabot Corporation, the world's largest manufacturer of nanoparticles. Extensive toxicology tests will be performed. Mechanisms of particle-cell interactions and potential adverse/beneficial effects will be evaluated.
- Federal agencies support meetings, symposia, and conferences such as the 2005 Frontiers in Aerosol Dosimetry Conference, the 2005 Materials Science Conference, and the NanoTox 2006 Conference as forums for nanoscience collaboration and dialogue.

Research/Information Needs

Understand the mechanisms of interaction between nanomaterials and the body at the molecular, cellular, and tissular levels. Cell culture systems and animal models indicate that some nanomaterials cause oxidative stress, inflammation, and immunogenic responses. Those reactions can lead to acute and chronic pathologies. However, studies of these systems and models are considered valid only for singular materials tested and at the specific doses tested. They may not identify the mechanism of action relevant to exposures or doses that might occur from use of other nanomaterials.

Understand the absorption and transport of nanomaterials throughout the body. A thorough understanding of nanomaterial physicochemical properties and their interaction with the body's molecular and cellular processes is essential to development of biocompatible nanomaterials. Although the translocation of nanomaterials through normally protective barriers in the body

may pose a hazard for certain environmental exposures, it may actually be beneficial for specific medical applications. For example, some studies link translocation of pulmonary nanomaterials into the circulatory system with cardiac and blood clotting effects. On the other hand, modifying the surfaces of nanomaterials may target them to specific locations in the body or actually promote or prevent their translocation throughout the body. Included should be epidemiological research on the development of atherosclerosis and vascular and blood biocompatibility. There is also a need for understanding the potential for accumulation of nanomaterials in organs and tissues of food-producing animals. To complete the ADME/Tox profile, it is important to identify the mechanisms of metabolism (especially breakdown of complex nanomaterials that contain multiple active moieties) and the routes of excretion.

Understand the long-term effects of implantable nanomaterials and other means of continuous exposure. Several nanomaterials have promise as scaffolding in bone repair and nerve regeneration and in replacement of degenerated knees and hips. Noninvasive techniques for monitoring the performance of these devices over their expected extended service (lifetime) are needed. Many of these devices will be subject to wear and degradation. The toxicity and clearance pathways of wear debris and degradation products need to be understood, and clinical indicators of adverse host response to the degradation products need to be identified.

Identify or develop appropriate *in vitro* and *in vivo* assays/models to predict *in vivo* human responses to nanomaterials exposure. Established *in vitro* and *in vivo* assays are available to measure the production of oxidative species, chemical species, DNA damage, genetic toxicity, inflammation, and immune function. These assays provide information on the most common biological responses to an exposure. Given the novel physicochemical properties of nanomaterials, however, the ability of *in vitro* systems to predict *in vivo* response needs to be monitored. It should also be noted that animal models do not always predict human biocompatibility and toxicity. Newer biotechnologies (e.g., genomics, proteomics, and metabolomics) provide research tools that may detect novel biological responses to nanomaterials and may suggest new and more effective types of assays. Standards for handling of nanomaterials for *in vitro* and *in vivo* testing are required, e.g., appropriate solvents and dosing formulations, methods to prevent agglomeration, and stability conditions. This will improve the reliability, reproducibility, and accuracy of the assays and methods used within a laboratory and among laboratories.

Integrate biological data on nanomaterials into predictive physiology-based, pharmacokinetic (PBPK) models of toxicity. A PBPK model is a mathematical description of the relationship between the physicochemical properties of a material and the physiological and pharmacokinetic responses in anatomically distinct regions or compartments of the body over time. Validated PBPK models with good predictive power may be used in risk assessment to identify potential target organs, predict disposition of a new material, and set research priorities.

Understand generalizable characteristics of nanomaterials in relation to toxicity. Initial research suggests that some properties—surface area, charge, specific surface modifications—may have general relevance to understanding nanomaterial toxicity. There is a need to collect and extend this information to support decision making regarding new nanomaterials, perhaps along with structure-activity relationship (SAR) modeling. SARs are increasingly being used for the analysis of chemicals to identify molecular features/attributes of concern that influence the biological activity of a given molecule.

Develop integrative databases of engineered nanomaterial properties and effects. Information regarding the physical properties, fate, and effects (biological and environmental) of nanomaterials is obtained through research and in the course of commercial development of nanomaterials. There

is potentially great value in collecting and integrating these data in ways that extend scientific understanding beyond that gained in individual experiments. However, the range of properties across material chemistries, shapes, and sizes is potentially so vast that synthesis of information within individual research efforts presents a daunting task.

It would therefore be worthwhile to consider development and maintenance of an integrative database that could combine and relate data across experiments in an open framework. Research is needed specifically to define a process for capturing data from disparate sources, to explore relationships of data types with respect to properties and biological or environmental effects; to synthesize information in ways that support risk management decision making; and to establish management approaches for updating and maintaining these databases. The NNI agencies, industry, and academia all will contribute to the research required to develop such capability (which is needed in many fields of scientific and commercial endeavor).

Determine the applicability and adequacy of existing occupational and environmental particle/particulate health effects databases to predict or assess the biological and health effects of engineered nanomaterials. One major research issue relates to the utility or adequacy of health effects and toxicological information derived from published literature and reports on occupational and environmental health effects. A particular question relates to the utility of existing data from air-particulate-matter research for a variety of natural and manmade processes. Arguments for use of this information include the potential for substantial insight from existing epidemiologic and mechanistic research. Arguments against this approach include the confounding effects of impurities and the lack of uniformity in particle size.

Possible Research Approaches

Understanding the characteristics of biocompatibility and toxicity may require some new tools, methods, and metrics. Development of tools—especially nondestructive methods—that measure particle size and quantity within cells and tissues will be critical to the success of bioeffects research. Such tools are essential for exploring the relationships between environmental exposure, absorbed dose, and effective dose.

Multidisciplinary research teams that combine expertise in physical and biological sciences will be critical for understanding the relationships between nanomaterial physical characteristics and the exposure, uptake, and biology at the systemic, organ, cellular, and molecular level. One major goal of a multidisciplinary approach is elucidating important determinants of biocompatibility and toxicity that require measurement, so as to enable these determinants to be applied across classes of nanomaterials. Multidisciplinary studies would also inform appropriate measures for exposure and benefit/risk analysis and assessment, and risk management. Model multidisciplinary programs are now under way at several NNI agencies, including EPA, NSF, and NIH.

EXPOSURE: ROUTES AND MEASUREMENT

Dose in a biological system is difficult to measure directly, so exposure is commonly used as a surrogate. Exposure is frequently measured at the border between the environment and the biological system as a mass concentration (e.g., milligrams per cubic meter of air). The exposure-response relationship is a key to understanding the safety of nanomaterials. Determining the doses, or quantities, of a material that will cause physiological responses in humans resulting from exposure requires the knowledge of the physicochemical properties of the material, the exposure conditions, the deposition and clearance, and the susceptibility of the system or person to the exposure. The type

and magnitude of a biological response to a nanomaterial indicate the biocompatibility or toxicity of the nanomaterial.

Selected Relevant Federal Government Actions

EPA's 2003, 2005, and 2006 STAR grants and current intramural research efforts are examining the detection, dosimetry, and fate of nanomaterials in complex biological systems following dermal, oral, and inhalation exposures as well as cellular interactions and uptake. For example, pulmonary and gastrointestinal toxicity studies involve the determination of the potential fate of nanomaterials that enter the body via inhalation or ingestion, respectively, and their translocation throughout the body (es.epa.gov/ncer/nano/research/index.html). EPA's Nanotechnology White Paper (U.S. EPA, 2005) identifies research needs that will lead to a strategy to complement, enhance, and integrate EPA's intramural and extramural efforts to address research needs associated with nanomaterial detection, dosimetry, and fate in biological systems.

EXPOSURE ROUTES

Assessing exposure to nanomaterials requires understanding relevant routes of exposure. For a material (nanoscale or otherwise) to induce a measurable biological response, it must enter the body, usually through the respiratory tract, skin, eyes, or digestive tract, or through intravenous exposure of patients and healthy donors, and reach an appropriate site in the body at sufficient concentration and for a necessary length of time. The relationship of exposure to uptake differs for each route of exposure and is a function of the physicochemical characteristics of the material and the structure and function of the organ or system that acts as the entry point. To date, there is little research on human cells and systems, and questions exist regarding the best animal models for anticipating human impacts, particularly those related to dermal exposures.

The respiratory tract. The upper airways of the lungs have a relatively robust protective cellular layer (epithelium), but the alveoli (regions of the lungs where gas exchange occurs) are deeper and more vulnerable. Research has shown that discrete nanoscale particles (those smaller than 100 nm that do not agglomerate, as many do) deposit at higher concentrations in the alveoli, whereas agglomerated materials with diameters larger than 100 nm deposit at higher concentrations in the upper airway. (There is evidence that there is at least partial clearance of these materials by normal macrophage processes from both lung regions, but some materials may escape macrophage identification.) Animal research also has demonstrated that nanoscale particles can be taken up by sensory nerve endings within the airway epithelia, followed by axonal translocation to ganglionic and central nervous system structures. For example, as noted earlier, rat studies have shown that inhaled or intranasally instilled nanoscale graphite can be transported via the olfactory nerve to the olfactory bulb (Oberdörster et al, 2004; International Commission of Radiological Protection, 2003).

The skin. The skin has a strong external barrier, the stratum corneum, which protects sensitive internal organs from environmental exposures. Healthy skin is generally considered impervious to particle exposures. Some studies have shown some nanomaterial accumulation in the hair follicles, penetration of sebaceous glands, or movement through the lipid pathway located between the cells of the stratum corneum, but, again, not penetration through the external skin layers (Bennat, Müller-Goymann, 2000). With regard to specific nanomaterials, several unpublished studies suggest that nanoscale titanium dioxide does not penetrate the skin (RS/RAEng, 2004). Other research using quantum dots with porcine models showed evidence of the materials entering the epidermis and dermis through intact stratum corneum (Ryman-Rasmussen et al, 2006) and through compromised strateum corneum in mouse models (intradermal injection), resulting in translocation of the quantum dots to

the lymph nodes and liver (Gopee et al, 2006). The relationship between the dose of nanomaterial to which the skin is exposed and the dose absorbed into the skin is not well understood.

The digestive tract. Particle uptake in the digestive tract has been well studied, mostly for drug delivery. This complex system absorbs macromolecules at numerous points along its length. Several studies demonstrate uptake of nanomaterials, including organ-specific targeted uptake that utilizes surface modification as the targeting methodology. Nanomaterials also can be ingested when they are transferred from hand to mouth, and ingestion accompanies inhalation exposure when particles are cleared from the respiratory tract via the mucosociliary escalator (International Commission of Radiological Protection, 2003).

Injection or Implantation. Particles may be injected into a patient via the subcutaneous, intramuscular, or intravenous routes, or may be injected directly into a tissue, organ, or tumor. Injected particles may be intended to target specific organs, tumors, and diseases or may serve as imaging and diagnostic agents. The disposition and biocompatibility of the particles will depend on ADME/Tox profiles—which are known to be tightly linked to particle size and surface chemistry. Particles also be released from implanted devices, whether as a result of designed resorption or as a result of matrix material wear and degradation. These may accumulate in local tissues, be transported to filter organs, or be excreted.

Research/Information Needs

Understand the relationship between the properties of nanomaterials and how they affect uptake via lungs, skin, and digestive tract. The relationships between the absorption of nanomaterials into the body and the nanomaterials' properties such as size, surface chemistry, and agglomeration characteristics are largely unknown. For example, research has just begun to explore the uptake of nanomaterials by the olfactory mucosa and the effects of particle size and surface charge on absorption of nanoscale particles into and through skin. Intravenous exposure is an additional example of research needed in this area. Valid biomarkers of exposure and response, particularly if exposure is route-specific, would support this goal. Successful completion of such research will improve exposure assessment methods.

Assess body burden. The total quantity of material in a biological system at any given time is a function of absorption and excretion of the material; it is defined as the body burden. Traditionally, body burden is determined by elemental analysis, a quantitative technique requiring destruction of the biological material. Body burden is expressed as mass of the material per gram of body mass. However, for nanomaterials this traditional technique may not be a useful metric for assessing biological effects. The definition of body burden may need revision because of uncertainty surrounding the correct dose metric for nanomaterials. A new definition may be required that reflects, for example, novel properties, surface area, chemistry, particle number, or size distribution. The need for redefinition applies both to the measurement of body burden for *in vivo* studies and to cellular uptake studies *in vitro*. Few tools exist to analyze the nanomaterial particle number and size distribution in cells or tissues.

Understand the relationship between the matrix (the material within which the nanomaterial is used or delivered) and absorbed dose, including synthesis byproducts and other impurities. The forms and matrices within which nanomaterials will exist are likely to be as diverse as their applications. The byproducts of synthesis and application, such as metals, could affect biological response. For skin preparations, an active ingredient or contaminant could alter uptake and transport of nanomaterials via emulsions, capsules, or other nanoscale delivery devices designed to penetrate the skin barrier.

EXPOSURE MEASUREMENT

Although exposure measurements are typically based on mass, current research indicates that for at least some nanomaterials, mass may be less important than particle size, surface area, and surface chemistry (or activity) (Magrez et al., 2006). It is also likely that some classes of engineered nanoscale materials could have different, possibly unique, primary determinants of dose relative to toxicity. Accurate and useful measurement techniques are also important since agglomerated nanomaterials may either retain or lose their emergent properties—or take on new properties—thus affecting the potential biological response.

Research is ongoing to explore the relative importance of other exposure metrics and methods. This includes developing techniques for characterizing aerosols and particles in-line (i.e., during production/manufacture) or as products (such as methods for measuring the surface areas of nanometer-diameter aerosols and particles) and to quantify their composition and structure. Some challenges have arisen in attempts to measure exposure and dose of nanomaterials. These include the following:

Mass metrics. When considering mass as exposure and dose metrics, a critical question is whether it is most appropriate to measure the mass of individual particles (which are less than 100 nm in one dimension) or massed agglomerates (which may be larger than individual particles). The dynamics of nanomaterial agglomeration can play a critical role in determining the pulmonary deposition of respirable nanoscale material. Larger aggregates of particles tend to deposit within the airways, while dispersed nanomaterials often reach the alveoli.

Particle number metrics. The importance of particle number concentration as exposure and dose metrics is not clear from existing toxicity data. In many cases, biological response may correlate more closely to total particle surface area than to particle number. However, in some cases the number of particles depositing in the respiratory system or penetrating beyond the respiratory system may be important.

Surface area and chemistry metrics. Any material's biochemical reactivity is highly dependent upon its surface chemistry. Bioreactivity may be more pronounced in nanoscale particles, where, for a given number or mass of particles, the total surface area delivered is dramatically larger than the surface area of an equivalent number or mass of microscale particles. Studies in rodents have shown that the toxicity of some nanoscale particles correlates with increased particle surface area (Oberdörster et al., 1992, 2000; Tran et al., 2000), whereas other studies demonstrate no increase in toxicity with decreased size (Warheit, 2006).

Research/Information Needs

Develop methods to quantify and characterize exposure to nanomaterials. Nanomaterials differ in significant ways from traditional materials for which established measurement procedures and equipment exist. One factor involves instrumentation: in general, many available devices and methods cannot accommodate and analyze samples at the nanoscale. Another factor involves uncertainties regarding the appropriate parameters for sampling and analysis. Procedures for measuring traditional materials are based on the assumption that particle mass and bulk chemistry are the characteristics that most determine whether the material is likely to have adverse effects. For certain nanomaterials, current research suggests that mass and bulk chemistry may be less important than particle size, surface area, and surface chemistry (or activity) when examining exposure impacts. Potential methods and technologies for measuring exposures to airborne nanomaterials, such as instruments that measure particle number and surface area, need to be evaluated.

Develop methods to quantify and characterize nanomaterials in biological matrices. Biological matrices (both internal to the body and external) are complex optical, physical, and chemical environments that may change the surface chemistry of administered nanomaterials. For example, lung surfactant proteins may be applied to nanomaterials post-synthesis to prevent agglomeration or may adhere to nanomaterials in a random manner after the nanomaterials have made contact with fluids and tissues in the airways and lungs. Although many technologies can detect the presence of nanomaterials in tissues, technologies that can measure particle size, surface area, and biochemical status within an organism are not readily available. Analytical methods, particularly those that would enable the integration of exposure across exposure routes (e.g., those for biomarkers that would be indicative of inhalation, ocular, and dermal exposures), need to be explored and validated for quantification and characterization of nanomaterials in biological and other complex matrices (see also Chapter 2, Instrumentation, Metrology, and Analytical Methods).

4. Nanomaterials and the Environment

This area describes research aimed at identifying, understanding, and controlling the potential effects of engineered nanoscale materials on both relevant ecological receptors and the ecosystems that they occupy, and research on fate and transport of engineered nanoscale materials that leads to a better understanding of the mechanisms by which nanoscale materials enter, remain, degrade, and are transported through environmental media.

Environmental Hazard Characterization

Although much of the current research into nanomaterial hazards has focused on human health, the models employed in these studies also offer insight into hazards for the broader range of environmental biota. Ongoing toxicity studies at EPA, NIOSH, and the National Toxicology Program, for example, will produce useful information to help elucidate environmental hazards of nanomaterials. However, the complexity of environmental hazards extends beyond basic mammalian toxicology. Physiological differences among various aquatic and terrestrial animal classes will lead to unique considerations; for example, the gills of aquatic organisms and avian respiratory systems pose issues not addressed by studies on mammalian respiratory systems. Terrestrial and aquatic plant physiology differ even more from mammalian systems. Currently, very few nanomaterial toxicity or uptake/distribution studies have been conducted with aquatic or terrestrial species, and no chronic, full, or multigenerational life cycle studies appear in the literature.

Environmental Transport and Fate

Environmental exposure to nanomaterials may occur via air, water, or soil. While little is known about the airborne transport specifically of nanomaterials, substantial research has explored the dispersion of incidental ultrafine particles arising from such sources as exhaust plumes. Particulates whose sizes range between 1 and 100 nm will move as governed principally by diffusion, whereas the movement of larger particles will be more influenced by inertial and gravitational forces (in the absence of buoyancy forces such as turbulence).

Engineered nanoscale materials released into the atmosphere will diffuse from areas of higher to areas of lower concentrations. Nanomaterials mix and disperse rapidly, and their transport and concentration can be influenced by air movement. Nanomaterials often agglomerate into larger masses, depending on the number of particles and their mobility. Because both of these parameters tend to increase with decreasing size for a given mass concentration, agglomeration tends to increase rapidly at very small size ranges. The result of such agglomeration, however, may still be a nanoscale particle. For nanoscale particles, other factors such as surface charge and humidity may influence particle agglomeration and settling. Some types of nanomaterials could become attached to dust, pollen, or other airborne particulates. Particles larger than 1 μm tend to deposit on surfaces mainly through inertial impaction and sedimentation. However, for nanoscale particles, the main mechanisms leading to deposition will include diffusion and electrostatic forces.

Wastewater streams and runoff from areas around a manufacturing plant—or around a waste dump or another place where nanoparticles are used, discarded, or released—might transport nanomaterials into the environment. Solubility and stability largely determine how a material disperses in water. Researchers have shown that C_{60} fullerenes, which are considered virtually insoluble in water, form colloids that remain suspended in water (Andrievsky et al., 1999, 2002). Thus, even though particular nanomaterials are insoluble in water, their agglomerates may persist in solutions.

Complexation and diffusion affect how a material penetrates into soil. Researchers at Rice University have developed laboratory models that simulate freshwater aquifers using spherical silicate glass beads to investigate how eight different types of nanoscale carbon-based and oxide particles migrate thorough porous media. These researchers have found that the transport behaviors of these materials differ widely. Fullerol particles (hydroxylated C_{60}) displayed the highest mobility, whereas agglomerate C_{60} fullerene particles were among the least mobile under the specific conditions of the model aquifer system (Lecoanet, Bottero & Wiesner, 2004).

Nanoscale products might be intentionally released into surface and groundwater systems and aquifers or soil for beneficial purposes, such as cleanup of toxic spills. Light-activated nanoscale titanium dioxide particles are being investigated for removing organic compounds from various media. One field study examined the efficacy of bimetallic nanoscale particles to remediate groundwater contaminated with aliphatic chlorinated hydrocarbons (Elliot & Zhang, 2001).

Any complete knowledge about the environmental fate of nanomaterials must account for a host of factors including bioavailability, bioaccumulation, persistence, synergistic effects of nanomaterials with other contaminants or naturally occurring compounds, formation of toxic metabolites, mobility of the material from one media to another, water solubility and groundwater contamination, transformation of compounds, and ultimate fate in ecosystems.

Engineered nanoscale materials have shown sensitivity to their physicochemical environment. For example, small changes in the surface charge of nanoscale silicon wires produce dramatic changes in electrical conductance (Cui et al., 2001). Similarly, small pH changes can dramatically affect solubility, which may enhance or diminish agglomeration. The effect of such small transformations on nanomaterial reactivity, transport, or fate is not well understood. To date, most investigators have explored the effects of nanomaterials in natural environments such as forests or wetlands. Programs are also needed to explore the influences of aging or degrading nanomaterials in reactive environments such as waste treatment plants that employ incineration or chemical treatment. Changes in nanomaterials through these processes may result in new or unexpected exposures, or affect fate and transport in indoor or outdoor environments.

Selected Relevant Federal Government Actions

- EPA is funding research on environmental exposures and effects, including plants, microbial species, and other organisms in the natural environment. Studies are under way at the University of Florida and Arizona State University on aquatic ecosystems; at Purdue University, the University of Delaware, and Rice University on microbial populations; at the universities of South Carolina and California, Berkeley, on estuarine systems; and at the Georgia Institute of Technology and Rice University on soil systems.
- EPA is funding research at universities to examine the fate of nanomaterials such as quantum dots, carbon nanotubes and nanowires, and metal oxides in the natural environment.
- EPA and NIOSH are funding work on the dispersion of nanoscale particulate aerosols.
- EPA, through its STAR grants program, began funding research in environmental toxicity, fate, and transport in 2004. To date the agency has funded 15 projects in fate, transport, and exposure assessment, and five projects addressing environmental toxicity. Descriptions of these projects are available at www.epa.gov/ncer/nano.
- As discussed in Chapter 3, several of the NSF-funded Nanoscale Science Engineering Centers include research on issues related to health and environmental implications of nanotechnology. In particular, the Center for Biological and Environmental Nanotechnology at Rice University

is looking at the interface between nanoparticles and biological systems and is studying various environmental effects resulting from exposure to nanomaterials. NSF's networks of nanotechnology user facilities— the National Nanotechnology Infrastructure Network (NNIN) and the Network for Computational Nanotechnology (NCN)—are available for use by all researchers in academia, industry, and government who need specialized tools for nanomaterials characterization.

- In addition to its large centers and user facility investments, NSF's core programs and its Nanoscale Interdisciplinary Research Teams (NIRT) and Nanoscale Exploratory Research (NER) program announcements have resulted in a number of research grants related to addressing the impact of nanomaterials on the environment. Three examples follow:
  1. *Nano Carbon Particles in the Atmosphere: Formation and Transformation.* This project focuses on development of theoretical and experimental methodologies to describe the formation and heavier hydrocarbons and particle inception, their growth, and transport in the atmosphere. These methodologies are needed for study of fate and transport of nanomaterials in the environment.
  2. *Response of Aquatic and Terrestrial Microorganisms to Carbon-Based Manufactured Nanoparticles.* This research is investigating the effect of carbon-based manufactured nanomaterials on the ecology and toxicity of aquatic and soil microorganisms.
  3. *Nanoscale Size Effects on the Biogeochemical Reactivity of Iron Oxides in Active Environmental Nanosystems.* This project studies the size-dependence of biogeochemical processes in active environmental nanosystems. Active nanosystems comprising iron oxide nanoparticles and iron-reducing microorganisms influence natural biogeochemical cycles and can provide the basis for improved environmental remediation technologies. The study will include a quantitative kinetic analysis and modeling of surface coordination of adsorbed species and will focus on fundamental aspects of nanoparticle reactivity research.
- The Department of Defense supports research to enable physicochemical characterization and toxicology for water, air, and space environments as well as research to assess, avoid, and abate any adverse environmental or health impact from defense utilization of nanotechnology.

Research/Information Needs

Evaluate the potential for effects on the environment. Nanomaterials or their transformation products may generate indirect and unforeseen environmental effects, such as changes in pH or air quality, or photo-oxidative or catalytic effects on other chemicals in the environment. Additional research is needed to explore the effect of such factors on both biological and nonbiological environmental conditions.

Evaluate testing schemes for ecological effects. Research is needed to evaluate the current ecological effects testing schemes and test protocols for individual species (organisms, endpoints, exposure regimes, media, and analytical methods) in those schemes to determine their applicability for regulatory decisions on potential effects of relevant nanomaterials and their byproducts. A variety of different types of tests will be needed to address potential effects of nanomaterials on relevant ecological receptors. These include traditional toxicity tests that are both short term (acute) and longer term (chronic). They may also involve the development of other innovative and novel tests based on the unique properties of nanomaterials. A better understanding of the distribution of nanoscale materials and their byproducts in ecosystems is needed to determine potentially affected compartments, species, and other effects that are not easily predicted in such complex systems. For relevant animal and plant ecological species, there is a need to better understand the ADME parameters

for nanomaterials. There is also a need to better understand how structure-activity relationships can be developed or adapted for a broad range of ecological receptors (including relevant aquatic and terrestrial species) and to identify the major modes of action are for these receptors.

Understand exposure potential in aquatic systems. The propensity of aquatic organisms to bioaccumulate pollutants is likely to vary greatly across types of nanomaterials. Knowledge of the factors that contribute to bioaccumulation would aid in risk management decisions. Such knowledge could lead to the design of nanomaterials so as to avoid bioaccumulation of the materials or their byproducts. Studies of nanomaterials could include evaluations of chemical and biotic factors likely to influence bioaccumulation and toxicity of nanoscale materials in aquatic systems. To address this, EPA uses persistence, water chemistry (e.g., dissolved organic carbon and particulate organic carbon), and biotic (lipid content and trophic level) characteristics when calculating national bioaccumulation factors for organic compounds (U.S. EPA, 2003).

Develop standardized sampling methods relevant to nanomaterials in the environment. It is not known whether (or to what degree) current sampling and analytical methods for estimating levels of materials or contaminants released into environmental media can be used for sampling and analysis of releases of nanomaterials. Investigations may address diverse types of environmental media: air, water, soil, sediments, plant matrices, and animal matrices (such as blood, bile, and whole body).

Identify the determining factors affecting the transport of nanomaterials in the environment. Some data from preliminary studies suggest that environmental transport mechanisms and partitioning for nanomaterials may differ from those for corresponding larger materials. Consequently, existing methods must be evaluated and new test methods developed where needed.

Understand the transformation of nanomaterials under different environmental conditions. Chemical reactions such as oxidation, exposure to sunlight, or exposure to moisture may change some nanomaterials. Microbially mediated biochemical reactions also can be expected to change the electrochemical and other properties of nanomaterials. Resulting changes may influence the behavior of nanomaterials in indoor versus outdoor environments. Studying the transformation of nanomaterials by the environment requires a comprehensive assessment of reactive environments (such as indoor, outdoor, aqueous, dry, and various lighting environments).

Other important research questions concern mechanisms by which nanomaterials may enter, remain, and move through the environment. These include the following:

- What factors affect atmospheric long-range transport and deposition of nanoscale materials?
- What quantities of nanomaterials enter the environment from workplaces and consumer products?
- What factors affect the potential for nanomaterials, if released either to exposed soil or in a lined landfill, to migrate to groundwater and to reach drinking water supplies?
- What factors affect the potential for these materials to be transported while bound to sediments or sludge in surface waters?
- How do aggregation, sorption, and agglomeration of nanomaterials affect transport processes?
- What factors affect the ability of nanomaterials to alter the mobility or reactivity of other substances in the environment?
- What biotic or abiotic processes affect persistence of nanomaterials in the environment or cause them to degrade? If they degrade, what are the byproducts and their characteristics?

Possible Research Approaches

Approaches to ecological and environmental effects testing should include representative nanomaterials from the major classes of commercial products, particularly those that are most likely to be released into the environment. Current ecological effects testing schemes and associated protocols should be evaluated with respect to their applicability to nanomaterials (including order of tests and criteria for proceeding from one test to the next in relevant testing schemes; as well as considerations of organisms, endpoints, exposure regimes, media, and analytical methods employed for individual protocols). Research on model ecosystems such as microcosms and mesocosms could provide indications of relevant ecosystem compartments, parameters, and species. ADME parameters, structure activity relationships, and modes of action should be determined for appropriate terrestrial and aquatic environmental receptors.

As with any new material, research on nanomaterials in the ecosystem will benefit from interdisciplinary collaboration. Interdisciplinary research teams should assess the potential of nanomaterials to disperse to various environments, with an eye toward assessing any effects resulting from the exposure of potential biological receptors in these environments. Research solicitations cosponsored by several Federal agencies requiring teams of chemists, material scientists, geochemists, microbiologists, and civil and environmental engineers may be necessary to understand the complex and interwoven issues involved in environmental fate of these materials. In addition, considering the volume and breadth of information likely to be generated, coordination among government, academic, and industrial researchers will help validate research data and apply results.

To gain a complete picture of ecosystem habitats and alterations attributable to exposures to nanomaterials, it will be crucial to start with laboratory research and end with pilot field studies. In addition, fundamental information regarding the nature or the differences between specific nanomaterials and their macro counterparts will be useful. Where possible, research should also focus on combining analyses on a system level, to learn about the mode and duration of any nanomaterials' alteration of various ecosystems.

5. Health and Environmental Surveillance

This area addresses research on the systematic collection, analysis, and interpretation of data obtained over time on human exposure to nanomaterials in the workplace and other indoor and outdoor environments; research to determine the presence of these materials or their byproducts in the environment; research on the determinants of exposures to support interpretation of limited or surrogate workplace and environmental data; monitoring of the health experience of individuals exposed to nanomaterials; and monitoring outcomes in habitats impacted by nanomaterials.

Health and environmental surveillance data are used to guide efforts to improve safety, health, and environmental protection and to monitor trends and progress. Health surveillance is a basic tool for Federal, state, and local public health and environmental protection activities. It can focus on a specific adverse outcome to identify risk factors or on a specific risk factor to identify adverse outcomes. The information can be used to characterize the extent of health and environmental problems, identify opportunities to prevent adverse effects, plan for delivery of services to mitigate the effect, and identify associations between adverse effects and possible causes that can serve as hypotheses for further research. Key to surveillance is the dissemination and use of data to protect health and the environment.

OCCUPATIONAL HEALTH AND EXPOSURE

To balance management of nanomaterial exposures, there must be consideration of possible unknown health effects that could occur despite caution in both the interpretation of existing toxicology information and in exposure mitigation measures. Health monitoring should be considered early in the nanomaterial development cycle for workers in selected applications where exposures are possible, even when controls for releases and exposures are in place. Many industrial firms already practice this approach. For nanomaterials, the emphasis of such monitoring programs should be on early detection of effects, and, where possible, should build on common properties across nanomaterial types.

Different work processes could produce substantially different exposures to nanomaterials. Workplace studies are under way for two primary purposes: to ascertain the nature and extent of current and emerging occupational exposures to nanomaterials, and to develop a comprehensive and scientifically sound occupational-health-protection strategy for nanomaterials. Information on typical exposure levels is important for risk analysis, prioritizing research, and planning protective actions to prevent similar exposures.

Selected Relevant Federal Government Actions

- The NIOSH Surveillance Program tracks occupational injuries, illnesses, hazards, and exposures (see www.cdc.gov/niosh/topics/surveillance/).
- The Bureau of Labor Statistics Injuries, Illnesses, and Fatalities (IIF) Program provides data on illnesses and injuries on the job and on worker fatalities (see www.bls.gov/iif/home.htm). It is intended to provide indicators of economic losses and does not collect medical diagnostic information.
- NIOSH has begun field research to inform the occupational safety and health community of the nature and extent of current and emerging occupational exposures to nanoscale materials.
- NIOSH is partnering with organizations to conduct field studies aimed at characterizing

exposures to nanoscale materials through a number of different mechanisms, such as its Nanotechnology Field Research Team visits of manufacturing facilities (see www.cdc.gov/niosh/topics/nanotech/newsarchive.html#fieldteam), the Health Hazard Evaluation Program (www.cdc.gov/niosh/hhe/HHEprogram.html), and research collaborations.

- NIOSH has initiated research to
  - evaluate the generation and control of engineered nanoscale materials at nanomaterial manufacturing and processing facilities
  - determine exposure concentrations (by mass, number, and surface area) for workers working with various nanomaterials
  - evaluate exposure assessment tools for nanoscale materials
- NSF has funded researchers at the University of Minnesota to perform experimental and numerical simulation of the fate of airborne nanoparticles from a leak in a manufacturing process to assess worker exposure.

Research/Information Needs

Collect health information. Injuries, illnesses, and clinical findings from employees are useful in identifying sentinel events or an unusual pattern of health outcomes. A sentinel event is a single case of an unusual injury or illness that is suspected of being associated with exposure to nanomaterials. Health data can be collected from company medical records or through health history questionnaires. If toxicity testing or other information identifies a concern for a specific health outcome, the results of medical monitoring for early clinical evidence of the outcome can also be collected and analyzed.

Collect exposure information. Exposure information can be highly qualitative such as "ever exposed (yes/no)," semi-quantitative such as "estimated level, time exposed, or exposure frequency," or quantitative such as "personal exposure monitoring data." Exposure data must be linked to the individuals so that it can be used to place individuals into exposure categories. Misclassification of individual exposures would reduce the ability of surveillance to detect health effects by reducing the difference between high- and low-exposure groups. Quantitative exposure data reduces the chances of misclassification and improves the quality of health surveillance programs.

Understand workplace processes and factors that determine exposure to nanomaterials. How nanomaterials behave in processes and the workplace factors that determine the exposures to nanomaterials need to be investigated as a foundation for developing effective exposure classification strategies. Exposure monitoring will evolve over time as knowledge and technology improve. Information on the process, task, and location variables that determine exposure in workplaces can be used to help reinterpret old monitoring data in the light of new knowledge or to classify exposures in a workplace that has not been monitored.

Analyze injury and illness reporting. Evaluations of existing occupational injury and illness reporting programs are needed to determine the feasibility and utility of their use for identifying adverse outcomes associated with nanomaterials. The key question is whether the programs collect information that allow for the identification of events associated with nanomaterials.

Possible Research Approaches

Injury and illness reporting. Existing occupational injury and illness reporting programs may have the potential to provide information on adverse events associated with nanomaterials; however, these are generally passive surveillance programs that rely on reporting of events requiring medical care

or identified on death certificates. Separate analyses of the data reported to these programs, with the goal of identifying events potentially associated with nanomaterials, would help ensure events are not missed. Individual companies or industry associations can voluntarily set up occupational injury and illness reporting systems that have a lower threshold for reporting and more detailed reporting. Analyses of injury and illness reporting systems could help identify sentinel events or patterns of events associated with nanomaterials that could then be investigated to determine cause and prevent reoccurrence. Passive surveillance is generally ineffective in identifying long-latency-period health effects or health effects that do not cause an individual to seek medical attention.

Occupational exposure registry. Exposure registries allow for the analysis of the health and exposure data for possible associations. Employment processes generate records on job duties, locations, exposures, and health status that can be used to establish an occupational exposure registry. These records may be augmented with special medical and exposure monitoring studies if the data are not already being generated by company safety and health protection programs. Suspicious health events or patterns of events can be investigated to identify possible associations with exposure. Proving causation generally requires additional study to establish the statistical significance of associations and a biological mechanism for observed health effects. Investigators usually must have access to medical records to code diagnoses to ensure actual rates can be compared to expected rates. Access to and protection of personal medical data must conform to medical confidentiality and privacy protection rules. Exposure-related data should be combined with data from sources such as the Nanoparticle Information Library (www2a.cdc.gov/niosh-nil), and with toxicity data to provide relevant information for risk assessment and risk management processes.

Cohort epidemiology studies. Hypotheses generated through surveillance or laboratory research can be investigated through studies that determine whether the incidence of a health effect among employees is elevated above expected rates. Individuals enter the studies on the basis of exposure and non-exposure. Population groups followed in an epidemiological study are often called cohorts. Cohort studies can be either prospective or retrospective and are used to determine if a health effect is associated with exposure and to quantify the relative risk associated with exposure.

Nested case-control epidemiology studies. Participants are selected based on health status and include a *case group* of individuals with a particular health problem and a *control group* of individuals free of the problem. These groups are analyzed to determine their actual exposure levels or the presence of other risk factors and then compared. Findings can be extrapolated to the population from which the cases and controls came. Risks are expressed as odds ratios that quantify the degree of risk associated with an exposure level or other factor. Nested case-control epidemiology studies often follow cohort studies to better understand the exposure levels or factors that caused an observed excess disease incidence.

PUBLIC HEALTH AND EXPOSURE SURVEILLANCE

Currently, little is known about the number, identity, health, or exposure levels of individuals who use nanomaterials or have close contact with users of nanomaterials (e.g., their family members). Similarly, little is known about how nanomaterials are released into the environment and their effects on exposed populations. The lack of descriptive information complicates the planning and prioritizing of research and protective actions. Collecting and analyzing health and exposure data for individuals exposed to engineered nanoscale materials, their precursors, and byproducts could help characterize the extent of health risks and ensure that risks are not overlooked through sole reliance on toxicity tests using animal models. Moreover, routine analysis and dissemination of health and exposure data can minimize the time needed to identify potential problems and to share lessons for preventing adverse events.

Selected Relevant Federal Government Actions

- The Centers for Disease Control and Prevention (CDC) coordinates with state and local health departments to operate a broad range of health surveillance projects. CDC's Toxic Substances and Disease Registry operates surveillance programs for environmental health effects (see www.atsdr.cdc.gov/about.html). Specifically, the National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the U.S. population's exposure to environmental chemicals using biomonitoring. Biomonitoring is the assessment of human exposure to chemicals by measuring the chemicals or their metabolites in human specimens such as blood or urine (see www.cdc.gov/exposurereport).
- The CDC collects information on environmental chemical exposures to the U.S. population through the National Health and Nutrition Examination Survey (see www.cdc.gov/nchs/data/nhanes/nhanes_03_04/blood03_04.pdf).
- The FDA maintains post-marketing surveillance programs for foods, cosmetics, medications, and medical devices to identify adverse events that identified after product introduction. Each center of the Agency maintains its own listings and websites, which can be accessed at www.fda.gov/nanotechnology.
- The Consumer Product Safety Commission (CPSC) operates an injury surveillance and follow-back system of a sample of hospital emergency rooms known as the National Electronic Injury Surveillance System to provide timely data on consumer product-related injuries occurring in the United States (ee www.cpsc.gov/library/neiss.html).
- The EPA Ambient Air Monitoring Group coordinates collection and analysis of air quality data from various air monitoring stations (see www.epa.gov/air/oaqps/organization/aqad/aamg.html).
- The EPA Watershed Assessment, Tracking & Environmental Results program coordinates the routine collection, analysis, and reporting of water quality data (see www.epa.gov/waters).
- The EPA has analyzed health studies, toxicological data, and exposure monitoring estimates for ambient particulate matter to assess their public health impacts (see cfpub.epa.gov/ncea/cfm/partmatt.cfm).
- The EPA's particulate matter risk assessments are a model for addressing questions concerning exposure, monitoring, and environmental fate. These would support similar assessments for engineered nanoscale materials. Ultrafine components of particulate matter (nanoscale particles) are a mixture of chemicals from combustion and natural sources, including gases that react with each other and precipitate to a solid state. Because similar chemical and combustion processes are being used to form first-generation engineered nanoscale materials, knowledge of ultrafine particulate matter may provide insight into dosimetry, fate, translocation, and physicochemical properties related to the toxicity of nanoscale engineered materials.

Research/Information Needs

Quantify nanomaterial exposure to the general population from consumer products, industrial processes, and products containing nanomaterials. Exposure assessment studies should be conducted to quantify any general population exposures to nanomaterials resulting from the use of consumer products. Nanomaterials may be released from these products, come in contact with humans, and be absorbed through various routes of entry (e.g., inhalation, dermal absorption) (Thomas, Sayre, 2006). Data should be collected to determine any accumulation and/or persistence of nanomaterials in the indoor environment, to characterize the exposure and identify changes to the nanomaterials (e.g., agglomeration), and to determine subsequent releases into the outdoor environment. The CPSC

Chronic Hazard Guidelines (57 Fed. Reg. 4633), the EPA Exposure Assessment Guidelines (U.S. EPA, 1992), and other relevant guidance should be used as appropriate in evaluating nanomaterial exposures in the general human population.

Analyze injury and illness reporting. The evaluation of existing injury and illness reporting programs for consumer exposures is needed to determine the feasibility and utility of their use for identifying adverse outcomes associated with specific nanomaterials. As in occupational exposure reporting, a key question is whether the programs collect information that allow for the identification of events associated with nanomaterials.

Identify population groups exposed to engineered nanoscale materials. Groups potentially exposed to nanomaterials include patients, consumers, and neighbors of production or utilization plants. Targeting surveillance on a potentially exposed group—and sensitive populations within groups, such as people with pre-existing health problems—requires identification of group members. Demographic information also is collected to allow for comparison of the cohort's injury and illness rates to expected rates for a group with similar demographics. Records of identifying information allow for longitudinal follow up of long-latency health outcomes and for notifying participants of indications that they should take actions to protect their own health.

Collect health information. Injuries, illnesses, and clinical findings from members of the at-risk cohort are collected to identify sentinel events or unusual patterns of health outcomes. (See the preceding section *Occupational Health and Exposure* for additional description.)

Collect exposure information. Exposure information can be highly qualitative such as "ever exposed (yes/no)," semi-quantitative such as "estimated level, time exposed, or exposure frequency," or quantitative such as "biomonitoring data or prescribed medications." Exposure data must be linked to the individuals in the at-risk cohort so that it can be used to place individuals into exposure categories.

Possible Research Approaches

Injury and illness reporting. The existing injury and illness reporting programs described above for non-worker exposures may have the potential to provide information on adverse events associated with nanomaterials. (Further discussion of issues involved in such reporting systems is included under "Possible Research Approaches" in the preceding section, *Occupational Health and Exposure*.)

Environmental exposure registries. Individuals are offered enrollment in environmental exposure registries if they are potentially exposed by living in impacted areas. Exposure registries analyze health and exposure data for possible associations. Proving causation generally requires additional study to establish the statistical significance of associations and a biological mechanism for observed health effects. Investigators usually must have access to medical records to code diagnoses for comparison of actual rates to expected rates. Access and protection of personal medical data must conform to medical confidentiality and privacy protection rules.

An environmental exposure registry follows the health of individuals exposed to contaminated air or water. If locations where releases of nanomaterials result in exposure, monitoring can estimate exposure levels and the exposed individuals can be enrolled in programs that gather health outcome data.

Cohort and nested case-control epidemiology studies. Epidemiology studies could be used to identify health effects associated with exposure. (Further discussion of these approaches is included in the section on Reducing Exposure in the Workplace in Chapter 6.)

ENVIRONMENTAL HEALTH SURVEILLANCE

Engineered nanoscale materials might enter the environment via effluents from large-scale manufacturing, use and disposal of personal care products, dispersive uses such as fuel additives, deliberate disposal, or transportation accidents. Nanomaterials also might be intentionally introduced into the environment in the process of pollution remediation. Nanoscale iron and palladium/iron particles are under investigation to remediate sites contaminated with hazardous chemicals such as trichloroethylene. Researchers have already tested some of these materials at sites (Mach, 2004; Zhang, 2003), but to date, little is known about the effects releases might have on the environment.

Selected Relevant Federal Government Actions

Currently, there are no Federal Government programs conducting surveillance of ecological health that focus specifically on nanomaterial releases or effects from them. However, there are many programs at agencies such as EPA, National Oceanic and Atmospheric Administration, and the U.S. Geological Survey (USGS) that regularly monitor and report the condition of aquatic and terrestrial ecosystems, as well as state programs. At EPA several programs are authorized by the Clean Water Act, including the Watershed Assessment, Tracking & Environmental ResultS (WATERS) Program and the biennial state water quality monitoring reports. The USGS National Water Quality Assessment Program, Toxic Substances Hydrology Program, and Contaminant Biology Program assess the health, or status and trends of contaminants in water and biota. These programs provide an infrastructure on which to build future efforts to monitor the impact of nanomaterials on environmental health. Such efforts must be built on a solid scientific basis and enabled by the types of research and information described in Chapters 2, 3, and 4 and in the remainder of this chapter.

EPA's Office of Research and Development is assisting with sampling and performance evaluation for a field test of nanoscale zero-valent iron at a U.S. Department of Defense site. The plans include monitoring the effects of the nanomaterials on bacteria that biodegrade contaminants on the site.

Research/Information Needs

Develop methods for measuring nanomaterial exposures in environmental matrices. Understanding potential environmental impacts from nanomaterial exposures begins with the means to quantify exposure. Development of environmental measurement methods should proceed in partnership with the evolution of toxicological understanding of exposure routes and bioavailability issues so that exposure monitoring methods can be targeted to the environmental media and chemical forms most relevant to understanding potential ecological risks (see also Chapter 2).

Establish environmental monitoring activities. Methods to monitor the environmental fate of nanomaterials should be developed to enable ongoing surveillance of air, water, soil, and sediments to establish the environmental exposures that occur as a consequence of nanomaterial use/release. (An example is monitoring at sites where nanoscale zero-valent iron is released into contaminated groundwater for treatment.) Where exposures exist, biological studies should be conducted to determine the effects of these exposures and the underlying mechanisms. Information on the type and amount of releases or changes in biota will help agencies prioritize questions that will benefit from further research. Disseminating summary information to nanomaterial industries and environmental protection agencies can promote early prevention activities.

Evaluate release scenarios most likely to create environmental exposures. This would be analogous to identifying susceptible sub-populations for human exposure; information on nanomaterial use and release must be combined with information on environmental fate and potential biological effects to determine where to target surveillance activities.

Determine environmental fate and effects following known or suspected releases. In cases where nanomaterials are used or disposed of in ways that create environmental releases, conduct focused studies to evaluate environmental fate. Where meaningful exposures exist, conduct studies to determine biological effects, if any, resulting from those exposures. Nanomaterials may affect not only the cellular processes of higher organisms, but also those of microbial communities that control organic decomposition, breakdown of contaminants, and other ecosystem services. Where possible, develop diagnostic tools to establish cause/effect relationships between nanomaterial exposure and biological effects.

Gain early knowledge of unanticipated effects to biota. Surveillance of biota involves the routine collection, counting, and evaluation of specimens in habitats affected by nanomaterials to identify abnormalities, population changes, or other effects requiring further investigation. Information on contamination in air, water, soil, sediments, and biological specimens related to engineered nanoscale materials, their precursors, or byproducts would be useful in identifying habitats to be monitored. The goal is to provide a "safety net" to identify circumstances where the environmental transport and behavior of, or the ecological effects of, nanomaterials are different from what would be predicted from existing knowledge.

Possible Research Approaches

Understanding emission sources and levels of concentration. It is common to monitor discharges from facilities to demonstrate compliance with environmental protection standards. Facilities researching, developing, and producing nanomaterials may need to monitor their air and water emissions to meet a regulatory requirement or may conduct this monitoring voluntarily. Such data provide information on the amount of material being emitted and can be used to estimate concentration levels in the surrounding environment. Monitoring methods similarly would need to be developed for nanomaterials.

Understanding levels of concentration and trends for nanomaterials in ambient air. Data from air monitoring stations near nanomaterial generating facilities might be able to provide information on releases of engineered nanoscale materials, their precursors, and byproducts if monitoring methods can be developed. Data on air quality from the EPA Ambient Air Monitoring Group's nationwide system of air monitoring stations could be valuable inputs to research in this area.

Understanding levels of concentration and trends for nanomaterials in surface and groundwater. The EPA Watershed Assessment, Tracking & Environmental ResultS program coordinates the routine collection, analysis, and reporting of data on water quality from local, state, and Federal water quality monitoring programs. Information from water quality monitoring stations near nanomaterial generating facilities or near watersheds that could be affected by nanomaterial facility operations might be able to provide information on releases of engineered nanoscale materials, their precursors, and byproducts if monitoring methods can be developed.

Collecting data from existing monitoring programs. On large government-owned military, industrial, and testing sites, such as Superfund sites, with activities involving hazardous materials, surveys are often performed on terrestrial and aquatic species to identify possible effects of their operations. Data from such routine monitoring programs, especially at sites that have used nanoscale environmental remediation methods or that are currently hosting other nanotechnology activities, might be used to identify effects of nanomaterials. Data collected by ecologists and others monitoring natural environments for other purposes could also be useful in understanding possible effects of nanomaterials at the ecosystem level.

6. Risk Management Methods

This area comprises research on methods for risk management of nanomaterials, including research on methods to reduce exposures to potentially hazardous nanomaterials; to improve procedures for risk and accident avoidance; to improve work practices, engineering controls, and protective equipment; and to develop procedures for life cycle assessment and improved understanding of potential impacts over the full product life cycle, from raw material extraction through disposal and/or recycling.

RISK MANAGEMENT APPROACHES

Once identified, risks traditionally are managed by taking one or more steps, beginning with simply replacing the use of a potentially hazardous material or process with one that is less so. As noted earlier in this document, some nanomaterials may offer safer alternatives to known hazardous materials in certain applications. Other methods for risk management involve reducing exposure, which includes protecting workers in manufacturing facilities, as well as controlling releases from such facilities, from transport vehicles, and from spills or accidents involving these materials. Potential exposure of the public to nanomaterials in consumer products must be considered for both the use and the disposal or recycling of products containing nanomaterials.

The research identified throughout this document will contribute to risk assessment and will guide risk management decisions. Current risk management techniques, even those used to minimize exposures to fine or ultrafine particulate matter, must be evaluated for their appropriateness in addressing the new uses and properties of engineered nanoscale materials.

An initial priority is evaluation of risk management techniques for workers in manufacturing and research facilities and for their potential applicability to larger populations. Uncertainties regarding potential hazards in handling specific engineered nanoscale materials have led NIOSH and the Occupational Safety and Health Administration (OSHA) to consider risk management approaches, such as control banding or risk management toolkit, that do not rely on traditional exposure-limit-based approaches. Such approaches are designed to allow unhindered innovation, while simultaneously ensuring the safety and health of the public and the environment. There may be other approaches for managing potential exposures of workers or others. Risk management approaches for nanomaterials will need to be evaluated as researchers continue to assess potential hazards and risks.

Selected Relevant Federal Government Actions

- In December 2004, EPA's Science Policy Council formed a Nanotechnology Workgroup to identify science policy issues related to nanotechnology and the environment. The workgroup determined that a white paper would be the appropriate product to provide information for EPA managers and to communicate the science of nanotechnology, science policy, and research issues of importance to EPA. The EPA Nanotechnology White Paper then was drafted, and underwent external peer review in the spring of 2006. It will be released as a final EPA document by the end of 2006. The external review draft of the White Paper may be found at www.epa.gov/osa. The risk management chapter of the EPA White Paper describes the framework and approach the agency envisions for managing the potential risks associated with nanomaterials. It includes discussions of environmental stewardship and pollution prevention, as well as authorities under EPA's existing statutes addressing protection of the air, water, and land.
- EPA held a public meeting on June 23, 2005 to discuss a potential voluntary pilot program for reporting information pertaining to existing chemicals that are nanoscale materials and the information needed to adequately guide the conduct of the pilot program. Following the meeting, EPA requested that the National Pollution Prevention and Toxics Advisory Committee

(NPPTAC) consider providing input to EPA on options for elements of EPA's approach to such a program. NPPTAC considered comments received during the June EPA public meeting and held additional public meetings to obtain broad stakeholder input. An Overview Document on Nanoscale Material, which presented the NPPTAC analysis and views of a framework, was provided to EPA for consideration of an approach to nanoscale materials.

- FDA has formed an internal task force that will identify and recommend ways to address any knowledge or policy gaps that exist so as to better enable the agency to evaluate possible adverse health effects from FDA-regulated products that use nanotechnology materials. The task force wll chair a public meeting on October 10, 2006, to help FDA further its understanding of developments in nanotechnology materials that pertain to FDA-regulated products.
- NIOSH's Nanotechnology Research Center conducts research into the implications and applications of nanoscale materials for work-related injury and illness, including assessment and development of risk management techniques (www.cdc.gov/niosh/topics/nanotech/). NIOSH's Nanotechnology Field Research Team partners with nanomanufacturers in assessing effectiveness of risk management practices in the workplace to reduce exposures to nanomaterials.
- NIOSH and OSHA are active in evaluating the applicability of control-banding approaches to risk management of nanomaterials. NIOSH defines control banding as "a process in which a single control technology (such as general ventilation or containment) is applied to one range or band of exposures to a chemical (such as 1–10 mg/m^3) that falls within a given hazard group (such as skin and eye irritants or severely irritating and corrosive materials)" (see www.cdc.gov/niosh/topics/ctrlbanding/). The importance of this approach was recognized at the October 2004 International Symposium on Nanotechnology and Occupational Health (see www.hsl.gov.uk/capabilities/nanosymrep_final.pdf).
- NIOSH conducted a national control-banding workshop in 2005 to discuss planning and implementing control-banding strategies in the United States.
- NSF supports fundamental research on decision making, risk, and uncertainty as part of its Human and Social Dynamics portfolio. This research will yield insight into decision-making processes, loss and mitigation models, and risk perception that are most applicable to managing the risks associated with emerging technologies, including nanotechnology.

Research/Information Needs

Evaluate the appropriateness and effectiveness of current risk management approaches for identifying those nanomaterials with the greatest potential risks. Parameters for grouping nanomaterials by hazard and exposure potential will help in the evaluation of risk management frameworks to determine their effectiveness.

Evaluate the opportunities for greatest potential risk reduction through minimizing hazard or exposure to nanomaterials. Factors influencing the potential for exposure to, or contamination by, nanomaterials need further investigation.

Evaluate accepted risk management approaches for nanomaterials. The suitability of control banding and other risk management approaches need to be further evaluated with respect to working with nanomaterials in situations where insufficient information is available to apply traditional exposure-limit-based control strategies. Banding or tiered approaches to risk management for nanomaterials and byproducts that incorporate both the potential hazard and level of exposure should be further evaluated for the ability to effectively reduce risks to human health and the environment.

REDUCING EXPOSURE IN THE WORKPLACE

Because nanomaterials already being commercially produced, attention should be given now to data that support risk management decisions for the workplace. Methods for controlling potential exposures to airborne and liquid materials in the workplace (perhaps applied hierarchically) include process design and engineering controls such as containment and ventilation systems, work practices, administrative actions, and personal protective equipment. The adequacy of exposure controls for "free" (not fixed in a matrix) nanomaterials should be researched further, because potential for exposure to free nanomaterials is greater than for embedded nanomaterials.

PROCESS DESIGN AND ENGINEERING CONTROL

Process designs and engineering controls have been important elements for risk management in the realm of industrial chemicals. Appropriate storage, containment, and ventilation all contribute to exposure-management strategies. In order to evaluate the efficacy of workplace air supply systems for nanomaterials, more research is needed on whether nanomaterials accumulate in recirculated air. Suspension of materials in air depends on general persistence, size, surface charge, and other factors. The suspension of different engineered nanoscale materials is expected to vary widely. However, because of the small size and low mass of all nanomaterials, those that do become suspended in air are likely to behave in a similar way to gas molecules, moving randomly as a result of Brownian motion. In this regime, nanomaterials can diffuse rapidly and remain suspended in air for an extended period of time. Various combinations of containment and ventilation systems could serve as conventional engineering controls for separating an exposure source of engineered nanoscale materials in this "gas phase." These include the following:

- total enclosure of the process
- partial enclosure with local exhaust ventilation
- open areas with active exhaust ventilation
- general ventilation

Selected Relevant Federal Government Actions

- NIOSH is conducting studies to evaluate the effectiveness of engineering controls to reduce exposure to engineered nanoscale materials. NIOSH is also interacting with industry groups that are addressing this issue (see www.cdc.gov/niosh/topics/nanotech/strat_plan.html). The Nanoparticle Occupational Safety & Health Consortium, for example, is examining issues related to the efficacy of equipment and materials to protect workers or researchers (see www.nanotechproject.org/index.php?id=18&action=view&project_id=741).
- Several NSF awardees are developing instrumentation for monitoring nanoparticles, which could be useful for ensuring the proper operation of control technology in factories. Examples include instrumentation for *in situ*, real-time, high-resolution measurements of nanoparticle size distributions, chemical composition of nanoaerosols, and laser Doppler velocimetry in synchronous AC electric and acoustic fields to determine the size and charge of nanoparticles. These technologies could also be used to monitor nanoparticle emissions in the environment, providing critical information for the design and implementation of mitigation strategies.
- An NSF-supported Nanoscale Interdisciplinary Research team is investigating ceramic membranes for filtration of nanoparticles, which could be an important control technology for manufacturing processes involving aqueous nanoparticles.

Research/Information Needs

Improve understanding of the unique challenges for process design and engineering control systems applied to engineered nanoscale materials in air. Process designs and engineering controls that govern the release of engineered nanoscale materials to air, control their removal from air, or control their exposure to air should be explored. One particular need is for research to evaluate the effectiveness of existing and novel engineering-control techniques for engineered nanoscale aerosols.

Possible Research Approaches

Efforts should focus on developing criteria for selection, design, and testing of processes and for engineering-control techniques to reduce risk of occupational exposure to nanomaterials.

There may be methods for storing nanomaterials that would minimize unintended exposures or the likelihood of unintentional release of nanomaterials. Nanomaterials might be confined in liquid suspensions or fixed within a solid matrix, such as pellets (an approach currently being used by some nanomaterials manufacturers), without loss of useful properties. Careful attention to the design of production processes also might minimize exposures from fugitive releases during handling, recycling, and disposal.

Manufacturing processes also could be designed to avoid use of hazardous elements and chemicals in order to minimize the potential to cause harm to the environment or workers.

WORK PRACTICES

Conventional work practices and administrative controls used to control exposure to particulate matter include the following:

- control or reduction in number of workers and exclusion of non-workers from the workspace
- reduction in periods of exposure
- regular cleaning of walls and other surfaces
- prohibition of eating and drinking in contaminated areas

Approaches to Safe Nanotechnology: An Information Exchange with NIOSH is a draft guidance and discussion document that outlines current knowledge about the occupational health and safety implications and applications of engineered nanoscale particles, using internal and external research data (www.cdc.gov/niosh/topics/nanotech/safenano/). It also offers interim recommendations on occupational safety and health practices in the production and use of nanomaterials, including mitigation of potential workplace exposures. These interim recommendations will be updated and revised as newer data become available.

Selected Relevant Federal Government Actions

NIOSH maintains interim guidelines for safe work practices and interim administrative controls in the nanomaterial manufacturing and processing environment that are updated as information is developed through focused monitoring and research efforts of the agency, its industrial and academic partners, and its international counterparts.

Research/Information Needs

Understand the role and effectiveness of work practices and administrative controls in reducing exposures to nanomaterials as exposure and hazard information evolve. There is need to evaluate

further whether unique properties of free engineered nanoscale materials (e.g., unique aerodynamic properties and propensity to agglomerate) require the development of novel work practices and administrative controls.

Possible Research Approaches

Research approaches could include continued collaborative efforts to address research gaps identified in interim recommendations on occupational safety and health practices in the production and use of nanomaterials.

PERSONAL PROTECTIVE EQUIPMENT

No studies on testing the effectiveness of personal protective equipment (PPE) against nanomaterials have been published. Existing guidelines that may be useful include

- OSHA 3143 (1998), which describes industrial hygiene practices and the prudent use of PPE
- Existing standards on the penetration of liquid-borne contaminants through protective clothing
- ASTM standard F1671-03, which specifies the use of a 27 nm bacteriophage to evaluate the resistance of protective clothing materials to penetration by blood-borne pathogens

No filtration system can remove completely airborne particles from air streams. Even High Efficiency Particulate Air (HEPA) filters designed to remove 99.97% of the particles whose sizes are the hardest to remove (typically around 300 nm) will allow a very small amount of aerosol to pass through. Furthermore, the properties of both the filter (e.g., fiber size, thickness, microstructure) and of the nanomaterials (e.g., surface charge, surface chemistry, geometrical parameters) determine the effectiveness and performance of a particular filter.

NIOSH certifies particulate respirators by challenging them with particles in the size range which research has found to be the most penetrating. In accordance with 42 CFR Part 84.181(g), sodium chloride aerosols with a count median diameter of 75 nm or dioctyl phthalate aerosols with a count median diameter of 185 nm are used for this purpose. Larger particles are collected more efficiently by impaction, interception, and settling, whereas smaller particles (down to at least 2.5 nm) are collected more efficiently by diffusion or electrostatic attraction (Lee, Liu, 1982).

As nanomaterials get as small as the diameters of individual molecules (a few nanometers in diameter and below), more efficient filter penetration is anticipated, comparable to penetration of gases, due to a phenomenon called thermal rebound. Studies also have shown good collection efficiency for liquid droplets in high-efficiency filters for particles down to 4 nm in diameter (Van Osdell et al., 1990). A recent review of manufacturing techniques suggests that most engineered nanoscale particles are larger than 20 nm or quickly agglomerate into larger particles, which makes them more likely to be collected by filters (www.hse.gov.uk/research/rrhtm/rr274.htm). Nonetheless, some researchers have expressed concern that nanomaterials may be subject to thermal bounce, which may cause them to bounce from filter fibers rather than stick to them, and thus pass through the filter.

Well-designed mask filters also must incorporate a tightly fitting face seal or a well-designed filter housing, so that stray particles cannot pass around the filter and enter into inhaled or exhaust air. Work by researchers at the U.S. Army Research, Development and Engineering Command on a headform showed that leakage around a mask (i.e., simulated respirator fit factor) measured using sub-micrometer aerosol challenges (0.72 μm polystyrene latex spheres) was representative of vapor challenges such as sulfur hexafluoride (SF_6) and isoamyl acetate (IAA) (Gardner, Hofacre & Richardson, 2004). Having been performed on sub-micrometer particles, these studies are inconclusive with regard to implications for nanomaterials.

Selected Relevant Federal Government Actions

- The NIOSH Respirator Selection Logic (www.cdc.gov/niosh/docs/2005-100/) suggests consideration of the following when selecting an appropriate respirator:
  - physical, chemical, and toxicological properties of the contaminant
  - NIOSH Recommended Exposure Limit (REL)
  - when no REL exists, OSHA Permissible Exposure Limit (PEL)
  - other applicable (occupational) exposure limits

  Presently, data are sparse on engineered nanoscale materials relative to the first criterion. However, in 2005, NIOSH posted for public review a draft *Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide*, which sets new RELs for nanoscale titanium dioxide at 0.1 mg/m^3 (www.cdc.gov/niosh/review/public/tio2/). At the time of this document's publication, this remains the only proposed occupational exposure limit for nanomaterials.
- In 2005, NIOSH awarded a contract to scientists at the University of Minnesota for a laboratory study to examine the efficacy of filters for selected engineered nanoscale particles. In this study, the researchers observed that penetration of nanoparticles through filter media decreased as particle size decreased down to 3 nm due to electrostatic and other forces that attract small particles to the filter media, as expected by traditional filtration theory (Pui and Kim, 2006). No evidence for thermal rebound of nanoparticles in the size ranges 3–100 nm was found. NIOSH plans to continue studying the nanoparticle collection efficiency of NIOSH-certified respirators to validate these findings.
- NIOSH and other Federal partners are also working with industry to evaluate the efficacy of current personal protective equipment against nanoscale material exposures, even though the PPE may not have been specifically designed to protect against nanoscale particulates.
- An NSF exploratory research project is examining the use of fractal nanoagglomerates as new media for HEPA filters.

Research/Information Needs

Understand the efficacies of PPE against nanomaterials as exposure and hazard information evolve. This research would involve evaluating filtration, filter-housing and face seal, and protective clothing efficiency down to the lower range of nanomaterial diameters (<10 nm).

Develop filters and fabrics with improved capturing and regenerating/self-cleaning capabilities. Nanomaterial applications offer tremendous opportunities to improve occupational safety and health through development of safety equipment with enhanced characteristics.

Possible Research Approaches

Protocols for testing PPE and respirators to determine effectiveness against exposure to nanoscale particles should be evaluated and developed where appropriate. Specifically, respirator recommendations for nanoscale aerosols, including determining protection factors and evaluating tests for proper fit, would enable significant advances in the area of nanomaterial risk management.

MINIMIZING ENVIRONMENTAL EXPOSURE AND HAZARD

Prudent strategies should be explored as frameworks to mitigate environmental exposure to nanomaterials if hazards are identified for specific materials. Such strategies might include reducing releases to the environment, improving waste treatment, designing nonpersistent nanomaterials,

and selecting more environmentally safe alternatives. Those topics are detailed in other sections of this document. Research should explore both conventional techniques and novel strategies yet to be identified.

Reducing environmental impacts can be achieved by a variety of means, including the following:

- reducing industrial releases
- avoidance of and preparation for spills and other accidents
- creating and using materials to minimize toxicity potential
- designing products that minimize potential exposures to humans and the environment
- engineering materials that degrade into more benign compounds when released into the environment

REDUCING INDUSTRIAL RELEASES

Manufacturing processes may result in releases of nanomaterials to the air, water, or land. It must be determined whether potentially toxic nanomaterials are released and the levels of such releases. Where releases occur, the first and easiest step toward minimizing contamination of the environment is through reducing the levels of nanomaterials released at the source. Research is needed to explore techniques to limit emissions to the air and in effluent discharge. Research on the possible hazardous character of solid wastes from nanomaterial manufacturing also is needed, as is research on the best methods to dispose of any relevant remaining manufacturing wastes, in general. Research is also needed to determine if disposal and degradation of consumer products could result in the release of nanomaterials into the environment, requiring attention to controls for landfills, incinerators, and recycling facilities. Research should explore "green" designs for nanomaterial-derived products to limit the persistence of hazardous nanomaterials in the environment over their life cycle. Life cycle assessment efforts (covered later in this chapter) will complement these efforts.

Selected Relevant Government Actions

- EPA has funded over 40 projects through its STAR research grants program and Small Business Innovation Research program, focused mostly on applications of nanotechnology to detect, prevent, treat, or remediate conventional pollutants. Only a few of these studies have addressed pollution prevention or control in the nanomaterial or nano-product manufacturing process itself. Information on these EPA projects is available at www.epa.gov/ncer/nano.
- NSF has funded several studies of environmental, health, and safety aspects of nanomanufacturing, along with a large number studies on the application of nanotechnology to detect or remediate conventional pollutants. One example of NSF's "green manufacturing" efforts is a Nanoscale Interdisciplinary Research Team that is developing solvent-free techniques to enable environmentally benign manufacturing of high-surface-area nanostructured composites. Further examples of NSF-sponsored EHS awards are available at www.nsf.gov/crssprgm/nano/7a_fy2005_env_nsfweb_06_0223.xls.
- The National Nanomanufacturing Network (NNN), led by the NSF–sponsored Center for Hierarchical Nanomanufacturing, includes health and industrial hygiene aspects of nanotechnology as part of its "Nanomanufacturing and Society" activities.

Research/Information Needs

Determine whether any residual manufacturing wastes of concern are being created and, if so, which processes are associated with such wastes. Some nanomaterial production processes are believed to produce little if any waste. Other processes, however, may produce waste. Sampling

manufacturing emissions and effluent releases is necessary to determine if wastes are generated that are associated with nanomaterial production or utilization.

Where wastes of concern are being produced, determine the best methods for waste disposal. Information is needed on the ability of existing technologies and possible alternative technologies to capture or mitigate nanomaterial releases. Particular properties of nanomaterials that determine their potential for capture should be identified. Based on these properties, new control technologies can be developed. Properties of solid wastes from nanomaterial manufacturing that may cause them to be considered hazardous waste also should be identified.

Understand and develop manufacturing approaches that minimize environmental impact through "green design" principles. In a sense, this is "beginning with the end in mind." Research is necessary to investigate integrating the technological processes into the manufacturing processes that will reduce the potential for ultimate release of nanomaterials into the environment. This is consistent with principles applied in other industrial chemical synthesis processes.

Possible Research Approaches

Studies would generally focus on technologies for removing/disposing of engineered nanoscale materials from emissions and effluents, concentrating on certain particle types or sizes thought to be potentially hazardous. In the long term, research could explore alternative technologies tied to specific nanomaterial properties, such as size, structure, and reactivity.

"Green" manufacturing research strategies need to be developed in conjunction with industry to conduct such research effectively and to address the processes with the highest levels of potential releases or hazard.

CONTAINING SPILLS

Materials may spill during manufacture and use. Conventional methods for controlling spills are generally designed for, among other things, the spilled material's physicochemical properties, toxicity, and potential adverse effects to human health and the environment. Guidelines for designing processes and equipment for preventing and containing spills, as well as procedures for risk management, can be found in a number of references (AIChE, 1988).

Regulatory authorities have accepted the effectiveness of various spill mitigation systems for laboratories and manufacturing plants to address known chemical/material hazards. These systems range from large dikes around storage tanks, along with associated pumps and secondary storage tanks, to absorbents designed for specific hazardous chemicals.

Selected Relevant Government Actions

The National Oil and Hazardous Substances Pollution Contingency Plan (NCP) provides the Federal framework to respond to oil, chemical, biological, and radiological releases to the environment, which encompass both accidental and intentional releases. The NCP is contained in regulation at 40 CFR 300 and is administered by the EPA. The NCP supports the National Oil and Hazardous Substances Response System (NRS) with planning, coordination, and direct preparedness activities by EPA for inland areas and the U.S. Coast Guard for the coastal zone. Other Federal agencies, along with state and local officials, support the two lead agencies under their appropriate jurisdictions. Although EPA does not currently have in place a program specifically to address risk management for wastes containing nanomaterials, existing programs would allow flexibility for future efforts.

Research/Information Needs

Develop spill mitigation technologies and risk management procedures specific to nanomaterials. There are no standardized technologies—and limited risk management procedures—explicitly designed to control spills of nanomaterials. Until such technologies and procedures are available, nanomaterial manufacturers may benefit from conventional spill mitigation plans and technologies, possibly with modification. In the long run, proper characterization of nanomaterials is necessary to develop specific containment technologies and procedures.

Possible Research Approaches

Both short-term and long-term approaches to developing spill containment and mitigation strategies should be considered. At the outset, a study could survey existing risk management practices and control technologies in spill mitigation for conventional materials to evaluate their potential applicability to nanomaterials.

A parallel research agenda could evaluate new methods and equipment designed specifically for minimizing and containing spills of nanomaterials. Specific questions that could be considered include the following:

- Can current conventional technologies and risk management procedures for spills be used or adapted to prevent and contain nanomaterial spills?
- Are existing methods that use collectors (i.e., vacuum systems) with HEPA filters effective to clean up a spill of nanoscale solids? If not, would a wet vacuum system work?
- How would cleanup systems then be handled? What determines the disposition of the accumulated nanomaterial?
- What PPE would be suitable for use by operators during spill mitigation?
- What unique procedures might be necessary to deal with nanomaterials dispersing and settling on various types of surfaces/equipment?

PREPARING FOR ACCIDENTS RELATING TO COMBUSTION AND REACTIVITY

Some nanomaterials have displayed exceptional energetic release. For example, reactions (thermites) of nanoscale Al and MoO_3 have been shown to ignite over 300 times faster than corresponding micrometer-scale material (Granier, Pantoya, 2004). Nanoscale combustible material could present a higher risk than a coarser material of similar quantity (Institute of Occupational Medicine, 2004). Presently, there is insufficient information on the explosion risk associated with nanoscale powders to enable reasonable risk predictions. Based on what is known of other "inert" materials that become dispersed in air (e.g., explosive risks of powders or flours), or the increased hazards of aerosolized flammable liquids (e.g., gasoline), the risks with significant amounts of nanomaterials may be nontrivial. Systems of codes, standards, and industry practices exist to provide both the educated workforces and the highly engineered preventive and containment equipment needed to reduce the likelihood or consequences of severe accidents.

Research/Information Needs

Understand factors influencing flammability and reactivity. The results of flammability and reactivity testing in both bulk and nanoscale versions of the same material could be collected and analyzed for unusual or conflicting results that require further investigation.

Discern trends in effects or causality in accidents or other incidents that may relate to the sizes or novel properties of engineered nanoscale materials. The goal of accident and incident investigations and reporting is to identify the root cause of unplanned adverse events so that recommendations for actions that will prevent recurrence can be developed and communicated. Industry-wide voluntary reporting of lessons learned from less serious accidents and minor incidents has been a highly effective method of improving risk management within the commercial aviation, nuclear, and other high-hazard industries.

Possible Research Approaches

A research program should be designed to systematically investigate the physical and chemical properties of classes of nanomaterials related to safety issues such as fire and explosion. The program also should include research on fire suppression of nanomaterials.

NANOMATERIALS IN THE TRANSPORTATION SYSTEM

The Hazardous Materials Regulations (HMR) (49 Code of Federal Regulations Parts 172–180) defines a hazardous material as a substance or material that the Secretary of Transportation has determined is capable of posing an unreasonable risk to health, safety, and/or property when transported in commerce. Materials listed in the hazardous materials table (49 CFR 172.100) or those that meet the defining criteria established in the HMR (49 CFR 173) are hazardous materials in transportation. Some nanomaterials could meet the Department of Transportation (DOT) definition of a hazardous material. DOT requires that persons who offer a hazardous material into the transportation system determine the hazard class or division, select proper packaging, package the material in accordance with package manufacturer's instructions, and communicate the hazards via shipping papers, labels and markings, and placards when required. Should a nanomaterial require packaging not covered under the HMR, the person who offers the material may submit a request for a special permit from DOT. A special permit is a document that authorizes a person to perform a function that is not currently authorized under the authority of the HMR, such as using alternative packaging.

Research/Information Needs

Fully characterize the nanomaterial to determine its properties and allow for an accurate determination and classification if it is a hazardous material. This may result in establishing a unique proper shipping name and United Nations (UN) identification.

Identify and evaluate the appropriate packaging requirements. This research would evaluate the efficacy in maintaining proper package integrity to prevent reasonable chance of release or ignition of the nanomaterial.

Determine if there should be any limitations or restrictions when using certain modes of transportation. This research will determine if certain materials affect the operation of the vehicle or the transportation environment.

Determine how best to communicate the hazard to the emergency response community under real-world accident scenarios. This supports a broader research need to evaluate the efficacy of existing first responder techniques and develop appropriate guidance for inclusion in the DOT Emergency Response Guidebook.

LIFE CYCLE ASSESSMENT

In order to responsibly manage environmental and human health impacts from nanomaterials, there is a need to better understand potential impacts over the full product life cycle, from raw material

extraction through disposal and/or recycling. Life cycle assessment (LCA) is a useful approach for such "cradle to grave" evaluation of both the impacts of the nanomaterials themselves and the impacts from the consumption of other resources (e.g., energy and materials) in the extraction, production, delivery, packaging, use, and disposal of the materials and products.

Life cycle research, accordingly, focuses on the evaluation of resource use and the potential health and environmental effects of nanomaterials and nanomaterial-based products from the gathering of raw materials through the final disposition of those products.

Currently the life cycle impacts of nanomaterials are generally unknown. The environmental impacts of nanomaterials (and their degradation products) may be different from bulk materials, given the importance of size-related phenomena for nanomaterials. This is important to consider at all life cycle stages, but particularly at the use and disposal stages. Thus, the initial focus of LCA studies might be to address those nanomaterial life cycle stages that might differ in specific ways from those of bulk materials.

LCA studies generate an inventory of resources consumed and materials and chemicals emitted over a full product life cycle. This information can be used to identify human and ecological exposure potential based on the use, recycling, and disposal of products, and when, where, and how those exposures could occur. The information also can help to identify potential human health and ecological effects.

LCA studies are often comparative, evaluating the different impacts associated with comparable products or different ways of producing materials. LCA studies may be used to identify and target opportunities for risk management through materials selection, product design, manufacturing, process engineering, and/or recycling processes for overall life cycle environmental improvement.

A complete LCA requires a large amount of data and can be both time-consuming and costly. It requires data that may be unavailable for a rapidly developing sector, such as nanotechnology. Therefore, it may be important to develop new streamlined LCA approaches that incorporate estimation techniques and can intelligently handle uncertainty. Much of the data needs identified in the Chapter 2 subsection on Analytical Tools and Methods will be important to LCA studies. An inventory of nanomaterials and their uses, as well as databases of nanomaterial properties and effects, will greatly enhance work in this field, as will nanomaterial monitoring, environmental surveillance, and toxicity assessments, which are discussed elsewhere in this document.

In addition, material flow analysis (MFA) can be used to partition and understand the economy-wide cycles and ultimate fate and associated potential impacts of a given nanomaterial and the products they form. MFA is defined in different ways, but generally it is an analysis that describes the flow of materials into, within, and out of a system. MFA is particularly useful for nanomaterials to understand and partition the likely ultimate disposition of a given nanomaterial. Quantitatively estimating the economy-wide flow of the nanomaterial will illuminate how much is likely "lost" during manufacturing, dispersed during use, incinerated after use, and recycled. This, in turn, will highlight likely human and ecological exposure pathways and help to identify preventive strategies.

Selected Relevant Federal Government Actions

- Scientists from a number of Federal agencies are working with the International Life Sciences Institute, Health and Environmental Sciences Institute on a Nanomaterial Life Cycle Assessment team that will apply LCA methodology to products that contain nanomaterials. The assessment team will attempt to explore the ultimate fate of nanomaterials in the environment. Their efforts will include the evaluation of the inputs and outputs of materials and the associated environmental and human health impacts from specific nanomaterials, from raw materials acquisition and product manufacture through consumer use and disposal (www.hesiglobal.org).

- The EPA STAR Program has funded four research grants addressing life cycle assessment: Implications of Nanomaterials Manufacture and Use: Development of a Methodology for Screening Sustainability, Environmental Implications of Nanotechnology, Life Cycle Analysis Approach for Evaluating Future Nanotechnology Applications, and Evaluating the Impacts of Nanomanufacturing via Thermodynamic and Life Cycle Analysis.
- NSF and EPA funded a study of manufacturing processes for five nanomaterials, including quantum dots, carbon nanotubes, and buckyballs, comparing their potential environmental and health risks with other common industrial processes (see www.eurekalert.org/pub_releases/2005-10/ru-snp100405.php and cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/6156/report/F).
- USGS conducts materials flow analyses of metals and industrial minerals in commerce (minerals.usgs.gov/minerals/mflow/) and collects statistics on production, use, and recycling of these materials through its Minerals Information Team.
- An NSF Nanoscale Exploratory Research project is developing risk scenarios for the full life cycles of three types of nanoparticles currently manufactured in multi-ton quantities: endohedral metallo-fullerenes, titania nanoparticles, and carbon nanotubes. The project's broad interdisciplinary approach, including toxicity studies, life cycle analysis, hierarchical holographic modeling, and assessment of the existing regulatory framework, will serve as a model for identifying environmental impacts and risks of nanomaterials.
- Another NSF grantee is using life cycle inventory (LCI) and life cycle assessment (LCA) methods to evaluate the environmental footprints of nanomanufacturing technologies.

Research/Information Needs

Understand how LCA may be suitable and adaptable to engineered nanomaterials. LCA techniques may need to be modified for nanomaterials. To determine this, LCA practitioners will need to become familiar with engineered nanoscale materials, how they differ from bulk compounds, as well as how they are likely to be manufactured and where they are likely to be used. Similarly, nanomaterials researchers will need to become familiar with the requirements and data needs of LCA practitioners.

Understand the use of nanomaterials in products. Adequate information on the ultimate use of engineered nanomaterials must be known for LCA. Key questions are as follows:

- Will the material be bound into matrices?
- Is the resulting product a liquid, powder, or solid?
- How is the product used? Is dispersion likely? How might the material degrade?
- Are the potential exposure routes intended or unintended?

Determine the stages in a product's life cycle that introduce the greatest potential for risk. Exposures to specific engineered nanomaterials may vary considerably based on the stage in the product's life cycle, which may impact the level of risk associated with a particular stage.

Develop environmentally benign manufacturing processes that can reduce the potential impact of nanomaterials. Research into processes and methods that utilize nontoxic, non-hazardous raw materials and that result in more resource-efficient techniques is needed to avoid negative impacts from nanomaterials on human health and the environment.

Understand the flow of nanomaterials through the economy and ultimate disposition. This MFA analysis will enable systematic identification of potential emissions and strategies for avoiding emissions, as well as likely exposure pathways.

Possible Research Approaches

Current efforts by Federal agencies and other groups attempting to apply LCA techniques to engineered nanoscale materials should be reviewed, and research into improving LCA techniques should be considered. Because of the high costs of LCA methodologies, LCA experts, nanomaterial manufacturers, policymakers, scientists, and engineers must work collaboratively to ensure that the quantity and quality of data collected is appropriate.

The existing broad database for bulk compounds (the U.S. Life Cycle Inventory database at the National Renewable Energy Laboratory (see www.nrel.gov/lci/) initially could be used as a source of data on raw material-manufacturing processes and potential associated emissions. Collaborative efforts between industry and academia, where process and product-development data is shared with researchers in the LCA community, could supply data requirements for an inventory of nanomaterials in production. As the inventory of specific nanomaterials grows, more extensive or focused databases may be required.

Early comparative research on the effects of conventional versus engineered nanoscale material compounds during different stages in their life cycles will be very useful to LCA. LCA, in turn, will help to identify areas where nanomaterials might be able to reduce environmental impacts resulting from the use of other materials. The vast literature on particulate matter research could be especially informative here (see www.al.noaa.gov/AQRS/reports/srppm.html).

RISK COMMUNICATION METHODS

A critical element of effective risk management is communicating to potentially affected individuals a clear and relevant understanding of potential exposures and risks and, when faced with these uncertainties, to help those individuals make choices to reduce or avoid risk. Depending on the scenario, these potentially affected individuals may be, for example, workers, consumers, or residents who live in the vicinity of a factory. Risk communication models could be based on existing models for chemical (and pharmaceutical) incidents.

Risk communications with regard to existing nanomaterials must address workers in manufacturing and research facilities. Communications must include information on hazards and potential for exposure, as well as methods for managing risks. Although information gaps exist for nanomaterials, risk communications often involve probabilistic statements of risk for materials about which there is limited information. Further, management guidance also must be given even when incomplete information is available. Many technologies and products—for example, propane, household cleaning supplies, and electric power—have associated risks that are successfully managed by users.

Selected Relevant Federal Government Actions

- Federal agencies, including CPSC, FDA, EPA, and NIOSH, have notification mechanisms for communicating potential risks. An important part of CPSC's mission, for instance, is to inform the public about potential hazards from consumer products. The agency uses a variety of mechanisms to accomplish this, including local and national media coverage, publication of numerous booklets and product alerts, a website, a telephone hotline, the National Injury Information Clearinghouse, and CPSC's Public Information Center. The CPSC website also includes an interactive feature that allows consumers to report unsafe products and related injuries electronically. CPSC also maintains an email address (*info@cpsc.gov*) that can be used for inquiries about product recalls or to report potential product hazards.

For occupational settings, NIOSH can inform workers, employers, and safety and health professionals about newly identified occupational hazards through NIOSH Alerts (www.cdc.gov/niosh/alerts2.html).

- As noted earlier in this chapter, NIOSH has developed the document *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH* to address worker information needs and to raise awareness of potential safety and health concerns from nanomaterial exposures. The document addresses current and future research needs essential to the understanding of potential risks of nanomaterials to workers. It is currently being used internationally to inform workers of related hazards (see www.cdc.gov/niosh/topics/nanotech/safenano/).
- FDA and CPSC have posted information on their regulatory approaches to products containing nanomaterials (see www.nano.gov/html/society/EHS.htm).
- NIOSH, in addition to the guidance document *Approaches to Safe Nanotechnology: An Information Exchange with NIOSH*, mentioned above, has created *NIOSH, Nanotechnology and Occupational Safety and Health Research—Frequently Asked Questions*, which is also available on its website (see www.cdc.gov/niosh/topics/nanotech/faq.html).
- NIOSH's National Occupational Research Agenda (NORA) held 12 meetings nationwide in 2005 and 2006 on research needs related to occupational safety and health. Inputs from those meetings will be considered by NIOSH in forming and revising research and risk communications practices for nanomaterials (www.cdc.gov/niosh/nora/).
- The NNCO has a document on its website titled *Reporting Risk Assessment of Nanotechnology* to help reporters with media analyses of risk-related research (www.nano.gov/html/news/reporting_risk_assessment_of_nanotechnology.pdf). The NNCO, in conjunction with DOE, also held a media roundtable in Berkeley, CA, in March 2006 with risk assessment included as a key part of the agenda.
- The NNCO held a workshop, Public Participation in Nanotechnology, in May 2006 to explore methods for public engagement on nanotechnology-related issues. Information from this workshop will be used to assess risk communication needs and future public engagement activities.

Research/Information Needs

Evaluate whether current risk communications are adequate for known risks and for risks that can be anticipated from currently available information. Federal agencies will evaluate existing models for informing the public about product hazards and potential product safety issues surrounding the use of nanomaterials in consumer products.

Where necessary, develop effective methods to communicate risk or safety information to potentially affected populations. If, in addition to workers, potentially affected populations are identified, communication strategies should be evaluated to ensure that risk communications are effective.

Possible Research Approaches

Existing methods to collect and disseminate information about exposure-related data from nanomaterial production facilities and downstream users could be evaluated. If beneficial, information could be conveyed through appropriate risk communication research methodologies for new engineered nanoscale materials.

It is important for Federal agencies to inform the public of risk situations. The currently existing mechanisms for reporting product problems and/or defects are also likely to be the most widely used for nanomaterial-related products. In addition, new mechanisms that provide reliable information on claims about engineered nanomaterials might be required.

Glossary

ADME	Absorption, distribution, metabolism, elimination
ADME/Tox	Absorption, distribution, metabolism, elimination, and toxicity
ANSI (TAG)	American National Standards Institute (Technical Advisory Group)
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CPSC	Consumer Product Safety Commission
CSREES	Cooperative State Research, Education, and Extension Service (USDA)
DHHS	Department of Health and Human Services
DOC	Department of Commerce
DOD	Department of Defense
DOE	Department of Energy
DOS	Department of State
DOT	Department of Transportation
EHS	Environmental, health, and safety
EPA	Environmental Protection Agency
FDA	Food and Drug Administration (DHHS)
HMR	Hazardous Materials Regulations
LCA	Life cycle assessment
NCI	National Cancer Institute (NIH/DHHS)
NCL	Nanotechnology Characterization Lab (NCI/NIH/DHHS)
NCP	National Oil and Hazardous Substances Pollution Contingency Plan
NEHI	Nanotechnology Environmental and Health Implications Working Group of the NSET Subcommittee
NIEHS	National Institute of Environmental Health Sciences (NIH/DHHS)
NIH	National Institutes of Health (DHHS)
NIOSH	National Institute for Occupational Safety and Health (CDC/DHHS)
NIST	National Institute of Standards and Technology (DOC)
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NNIN	National Nanotechnology Infrastructure Network (NSF)
NRC	Nuclear Regulatory Commission
NSET	Nanoscale Science, Engineering, and Technology Subcommittee of the NSTC
NSF	National Science Foundation

NSRC	Nanoscale Science Research Centers (DOE)
NSTC	National Science and Technology Council
NTP	National Toxicology Program (DHHS)
OECD	Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
PPE	Personal Protective Equipment
STAR	Nanotechnology Science to Achieve Results (EPA)
USDA	United States Department of Agriculture
USGS	United States Geological Survey (Department of Interior)
WATERS	Watershed Assessment, Tracking & Environmental ResultS (EPA program)

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